Emergency Use Authorization (EUA) Amendment
for an Unapproved Product
Review Memorandum

Identifying Information

Application Type	EUA (Event-driven EUA request)
Application Number	28237, amendment 71
Sponsor	Novavax, Inc.
Submission Date	July 22, 2022
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Review Completion Date	August 19, 2022
Established Name/Other names used during development	Novavax COVID-19 Vaccine, Adjuvanted / NVX-CoV2373
Dosage Forms/Strengths and Route of Administration	A 0.5 mL suspension for intramuscular injection
Intended Use for EUA	Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)
Intended Population	Individuals 12 through 17 years of age

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Glossary

AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CMO	contract manufacturing organization
COVID-19	coronavirus disease 2019
CTM	clinical trial material
DMC	data monitoring committee
DP	drug product
DS	drug substance
DSMB	Data and Safety Monitoring Board
ECMO	extracorporeal membrane oxygenation
EUA	Emergency Use Authorization
FAS	Full Analysis Set
GBS	Guillain-Barre syndrome
GMT	geometric mean titer
hACE2	human angiotensin-converting enzyme 2
h/o	history of
HHS	US Department of Health and Human Services
ICSR	Individual Case Safety Report
IgG	Immunoglobulin G
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MH	medical history
mRNA	messenger ribonucleic acid
MSSR	Monthly Safety Summary Report
NP	nucleocapsid protein
NVX-CoV2373	Novavax COVID-19 Vaccine, Adjuvanted
O/E	observed-to-expected
PCR	polymerase chain reaction
PIMMC	potential immune-mediated medical conditions
PP-EFF	Per-Protocol Efficacy Analysis Set
PP-IMM	Per-Protocol Immunogenicity Analysis Set
PT	preferred term
RNA	ribonucleic acid
RR	relative risk
rS	recombinant spike protein
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCR	seroconversion rate
SMQ	Standardized MedDRA Query
SOC	system organ class
TGA	Therapeutic Goods Administration
UMC	Uppsala Monitoring Centre
VAERS	Vaccine Adverse Event Reporting System
VE	vaccine efficacy
VOC	variant of concern
VOI	variant of interest
VT	verbatim term

1. Executive Summary

On June 22, 2022, FDA received a request from Novavax, Inc (the Sponsor) to amend the emergency use authorization (EUA) for the Novavax COVID-19 Vaccine, Adjuvanted to include adolescents 12 through 17 years of age (abbreviated 12-17 years). The vaccine, also referred to as NVX-CoV2373, is a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) recombinant spike protein nanoparticle vaccine (SARS-CoV-2 rS) with Matrix-M adjuvant. NVX-CoV2373 is currently authorized for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 in individuals 18 years of age and older. The proposed primary series dosing regimen is two intramuscular injections at the dose level of 5 µg recombinant spike protein (rS) and 50 µg of Matrix-M adjuvant.

The EUA request includes safety, immunogenicity, and descriptive efficacy data from the adolescent expansion part of an ongoing multinational Phase 3 randomized, double-blind, placebo-controlled trial (Study 2019nCoV-301). A total of 2,247 adolescents 12-17 years of age were randomized 2:1 to receive NVX-CoV2373 or placebo. During the course of the study, COVID-19 vaccines authorized for emergency use became available, and participants (when eligible for vaccination per national and local public health prioritization recommendations) were offered the opportunity to cross over from the originally assigned study treatment to the other study treatment (vaccine or placebo) in a blinded fashion ("blinded crossover"). Immunobridging and vaccine efficacy analyses were based on participants prior to crossover.

Vaccine effectiveness in adolescents was inferred by immunobridging based on the measurement of neutralizing antibody titers against a clinical isolate of SARS-CoV-2, using a microneutralization (MN) assay. A total of 750 adolescent participants 12-17 years of age and 750 adult participants 18-25 years of age were randomly selected from the adolescent expansion and the adult main study, respectively, to provide approximately 400 participants in each age cohort for testing of neutralizing antibody titers (accounting for the 2:1 randomization and 20% non-evaluable rate). Neutralizing antibody titers at Day 35 (i.e., 14 days after the second dose of the initial vaccination series) in adolescents 12-17 years of age who were seronegative to anti-SARS-CoV-2 nucleoprotein (NP) antibodies/PCR-negative at baseline were compared to titers in adults 18-25 years of age in the immunogenicity cohort (seronegative/PCR-negative at baseline). The primary immunogenicity endpoints were SARS-CoV-2 neutralizing antibody GMTs at Day 35 and seroconversion rate (SCR, defined as the percentage of participants with a ≥4-fold difference in neutralizing antibody titers between Day 35 and Day 0). The statistical success criteria for demonstrating immunobridging of the neutralizing antibody response at Day 35 required a point estimate of the GMT ratio (GMR) ≥0.82, a lower limit of the two-sided 95% CI of the GMR >0.67, and a lower limit of the 95% CI of the difference in SCRs >−10%. A descriptive analysis of vaccine efficacy (VE) among participants who received 2 study vaccinations was also provided. The primary efficacy endpoint was the first episode of PCR-confirmed symptomatic mild, moderate, or severe COVID-19 occurring at least 7 days after NVX-CoV2373 Dose 2 in adolescent participants who were seronegative/PCR-negative at baseline (pre-Dose 1) .

Immunobridging statistical success criteria, as described above, were met. The GMR (i.e., adolescents 12-17 years of age versus adults 18-25 years of age) was 1.5 (95% CI: 1.3, 1.7). The difference in SCRs (i.e., adolescents 12-17 years of age minus adults 18-25 years of age) was −1.0% (95% CI: −2.8%, 0.2%).

As of the August 9, 2021 cutoff, a total of 16 cases of PCR-confirmed symptomatic mild, moderate, or severe COVID-19 with onset at least 7 days after the second dose were accrued during the pre-crossover period in the per-protocol population (n=1205 NVX-CoV2373 recipients and n=594 placebo recipients). Vaccine efficacy (VE) against PCR-confirmed COVID-19 was 78.3% (95% CI: 37.6, 92.5); 5 COVID-19 cases occurred in the NVX-CoV2373 arm and 11 in the placebo arm. All 16 cases were mild in severity; sequencing could not be completed in 7 cases due to low viral load, and the other 9 cases were identified as the Delta variant (B.1.617.2; AY.3).

Safety evaluations included solicited local and systemic adverse reactions (ARs) during the 7 days following each vaccination in the pre-crossover period; unsolicited adverse events (AEs) and medically-attended adverse events (MAAEs) from Dose 1 through the 28 days post Dose 2 in the pre-and post-crossover periods; and serious AEs (SAEs), and AEs of special interest (AESIs, defined as COVID-related AEs and potential immune-mediated medical conditions [PIMMCs]) in the pre- and post-crossover periods through an October 6, 2021, extraction date. The safety analysis populations included participants who received at least one dose of NVX-CoV2373 in the pre-crossover period (N=2,232; 1487 NVX-CoV2373, 745 placebo) or post-crossover period (N=2,018; 665 NVX-CoV2373 crossover, 1,353 placebo crossover). In the pre-crossover period, the median follow-up post-Dose 2 was 71 days; 85% of participants in the NVX-CoV2373 arm and 82% of participants in the placebo arm had safety follow-up for at least two months post-Dose 2. In the post-crossover period, the median follow-up post-Dose 4 was 30 days; 41% of participants in each treatment arm were followed for at least two months post-Dose 4.

Solicited ARs were reported by a higher proportion of NVX-CoV2373 recipients than placebo recipients, and more frequently after NVX-CoV2373 Dose 2 (local and systemic: 75.3% and 74.5% of participants, respectively) than Dose 1 (local and systemic*:* 65.5% and 55.3% of participants, respectively). Severe local and systemic ARs were more frequent after Dose 2 of NVX-CoV2373 (8.5% and 21.9% of participants, respectively) than after Dose 1 (1.5% and 3.7%, respectively); injection site pain/tenderness and fatigue/malaise were the most frequently reported severe local and systemic ARs, respectively. In both study groups, the most commonly reported ARs were injection site pain/tenderness, headache, fatigue/malaise, and muscle pain (myalgia). Most solicited reactions were mild to moderate and lasted 1-3 days.

One serious event of myocarditis in the adolescent expansion was reported in temporal relationship to NVX-CoV2373, and FDA considers this event to be related to vaccination.

Events of lymphadenopathy were infrequent but reported by a higher proportion of participants in the NVX-CoV2373 arm (0.9%). Imbalances in the following additional non-serious unsolicited events are suggestive of a causal relationship to NVX-CoV2373: fatigue (0.5% vaccine recipients vs. 0.0% placebo recipients), decreased appetite (0.3% vaccine recipients vs. 0.0% placebo recipients), arthralgia (0.2% vaccine recipients vs. 0.0% placebo recipients), injection site pruritus (0.2% vaccine recipients vs. 0.0% placebo recipients), and myalgia (0.1% vaccine recipients vs. 0.0% placebo recipients). Hypersensitivity reactions, namely urticaria, were reported in more participants following NVX-CoV2373 (0.27%) than following placebo (0.13%). Review of the data also identified a numerical imbalance in events of depression and suicidality, although a conclusion of causal association cannot be made based on available data. Subgroup analyses of safety data did not reveal any safety concerns across demographic groups. No deaths were reported during the study.

Based on the totality of the scientific evidence available at this time supporting the conclusion that the Novavax COVID-19 vaccine may be effective, and that the known and potential benefits outweigh the known and potential risks associated with the vaccine when used for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older, the review team recommends authorization of the Novavax COVID-19 vaccine under EUA for use as a 2-dose series (5 µg SARS-CoV-2 rS antigen + 50 µg Matrix-M adjuvant/ per dose, 3 weeks apart) in individuals 12 years of age and older.

2. SARS-CoV-2 Pandemic

SARS-CoV-2 is a zoonotic coronavirus that emerged in late 2019 and was identified in patients with pneumonia of unknown cause. SARS-CoV-2 is the causative agent of COVID-19, an infectious disease with respiratory and systemic manifestations.

The SARS-CoV-2 pandemic continues to present a challenge to global health and, as of July 18, 2022, has caused over 562 million cases of COVID-19, including 6.3 million deaths worldwide (Johns Hopkins Coronavirus Resource Center, 2022). In the US, more than 89 million cases and 1 million deaths have been reported to the Centers for Disease Control and Prevention (CDC) (CDC, 2022a). Of the total COVID-19 cases reported in the US to date, 4.7% occurred among individuals 12-15 years of age (CDC, 2022b). Among cases of COVID-19 in individuals less than 18 years of age from the COVID-NET network, 9127 have resulted in hospitalization (CDC, 2022c). As of July 18, 2022, 755 deaths from COVID-19 have been reported in the US in the 12–17-year age group (CDC, 2022b). Following EUA of the first COVID-19 vaccines in December 2020, COVID-19 cases and deaths in the US declined sharply during the first half of 2021. Since the original Omicron variant (designated as the BA.1 variant) spread rapidly around the world, the virus has continued to evolve and at the present time, several sublineages of Omicron are in circulation in various parts of the world. In the U.S., by late December 2021 Omicron BA.1 had become the dominant virus variant, replacing the previously dominant Delta variant. By early April 2022, Omicron BA.2 became the dominant virus strain in the U.S, but by late April to early May, Omicron BA.2.12.1 began rapidly spreading and became the dominant strain in the U.S. for a time. Most recently, two other Omicron sublineages, BA.4 and BA.5, which appeared in South Africa in March 2022, have spread to the U.S. and as of August 13, 2022, the Omicron BA.4.6, BA.4, and BA.5 sub-lineages comprised the majority of the tested strains in the US (CDC, 2022d).

Symptoms associated with SARS-CoV-2 infection in individuals less than 18 years of age are similar to those in adults, but are generally milder, with fever and cough most commonly reported (Irfan et al, 2021; Liguoro et al, 2020). Most children with COVID-19 recover within 1 to 2 weeks. Of the total COVID-19 cases reported in the US to date, 7.3% occurred among individuals 12-17 years of age (CDC, 2022b). Among cases of COVID-19 in individuals less than 18 years of age from the COVID-NET network, approximately 10,861 have resulted in hospitalization (CDC, 2022c). As of August 18, 2022, 770 deaths from COVID-19 have been reported in the US in individuals 12-17 years of age (CDC, 2022b). or some children, COVID-19 symptoms may continue for weeks to months after their initial illness. The most common underlying medical conditions among hospitalized children were obesity, neurologic disorders, and asthma. Following observation of an increased incidence of myocarditis in 2020 compared with 2019, several studies have suggested an association between COVID-19 and myocarditis (Murk et al, 2021; Daugherty et al, 2021). Myocarditis may also present as part of the multisystem inflammatory syndrome in children, usually 3 to 5 weeks after a SARS-CoV-2 infection.

3 Authorized and Approved Vaccines and Therapies for COVID-19

3.1 Novavax COVID-19 Vaccine, Adjuvanted

On July 13, 2022, the Novavax COVID-19 Vaccine, Adjuvanted was authorized for active immunization to prevent COVID-19 in individuals 18 years of age and older. The primary series consists of two doses administered 3 weeks apart.

Review of safety data from Study 301 submitted to support authorization in adults 18 years of age and older identified events of myocarditis and/or pericarditis within 28 days of administration of the Novavax COVID-19 Vaccine, Adjuvanted, which resulted in a warning for myocarditis/pericarditis in the current Novavax COVID-19, Adjuvanted fact sheet.

The safety and effectiveness data supporting emergency use authorization of Novavax COVID-19 Vaccine, including additional information on cases of myocarditis and pericarditis, are detailed in the decision memoranda available on the FDA website.

3.2 Comirnaty and Pfizer-BioNTech COVID-19 Vaccine

Comirnaty (COVID-19 Vaccine, mRNA) contains a nucleoside-modified messenger RNA (mRNA) encoding the viral spike glycoprotein of SARS-CoV-2 that is formulated in lipid particles. The vaccine is administered intramuscularly as two doses 3 weeks apart, with each 0.3 mL dose of the approved formulation containing 30 µg mRNA. Under Emergency Use Authorization (EUA), the vaccine is called the Pfizer-BioNTech COVID-19 Vaccine, and the formulation authorized for use in individuals 12 years of age and older contains 30 µg mRNA in each 0.3 mL dose. The Pfizer-BioNTech COVID-19 Vaccine formulation authorized for use in children 5-11 years of age contains 10 µg mRNA in each 0.2 mL dose. The Pfizer-BioNTech COVID-19 Vaccine formulation authorized for use in children 6 months through 4 years of age contains 3 µg mRNA in each 0.2 mL dose. During clinical development, the vaccine was called BNT162b2.

Comirnaty is approved as a 2-dose primary series for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older. The Pfizer-BioNTech COVID-19 Vaccine is authorized under EUA as: a 3-dose primary series for individuals 6 months through 4 years of age; a 2-dose primary series for individuals 5 years of age and older; a third primary series dose for individuals 5 years of age and older with certain immunocompromising conditions; a homologous first booster dose administered at least 5 months after completion of primary vaccination to individuals 5 years of age and older; a heterologous first booster dose administered after completion of primary vaccination to individuals 18 years of age and older (the dosing interval is the same as that authorized for a booster dose of the vaccine used for primary vaccination); and a second booster dose administered at least 4 months after a first booster dose with any FDA authorized or approved COVID-19 vaccine to individuals 50 years of age and older and individuals 12 years of age and older with certain immunocompromising conditions.

The Pfizer-BioNTech COVID-19 Vaccine safety and effectiveness data supporting approval of Comirnaty and emergency use authorization of Pfizer-BioNTech COVID-19 Vaccine are detailed in the decision memoranda available on the FDA website.

3.2 Spikevax and Moderna COVID-19 Vaccine

Spikevax, manufactured by Moderna, contains a nucleoside-modified mRNA encoding the viral spike glycoprotein of SARS-CoV-2 that is formulated in lipid particles. The vaccine is approved for active immunization to prevent COVID-19 in individuals 18 years of age and older. The primary immunization series consists of 2 doses administered 1-month apart. The vaccine is authorized for emergency use (as the Moderna COVID-19 Vaccine) as: a 2-dose primary series for individuals 6 months of age and older; a third primary series dose for individuals 6 months of age and older with certain immunocompromising conditions; a homologous or heterologous first booster dose administered after completion of primary vaccination to individuals 18 years of age and older (the authorized dosing interval for a homologous booster is at least 5 months after completion of a primary series, and the authorized interval for a heterologous booster is the same as that authorized for a booster dose of the vaccine used for primary vaccination); and a homologous or heterologous second booster dose administered at least 4 months after the first booster dose to individuals 50 years of age and older and individuals 18 years of age and older with certain immunocompromising conditions. Safety and effectiveness data supporting approval of Spikevax and authorization of Moderna COVID-19 Vaccine are detailed in the decision memoranda available on the FDA website.

3.3 Janssen COVID-19 Vaccine

The Janssen COVID-19 Vaccine is authorized for use in individuals 18 years of age and older for whom other FDA-authorized or approved COVID-19 vaccines are not accessible or clinically appropriate, or who elect to receive the Janssen COVID-19 Vaccine because they would otherwise not receive a COVID-19 vaccine. The vaccine is authorized for use in these individuals as a single primary vaccination dose and as a single homologous or heterologous booster dose (the dosing interval for a homologous booster is at least two months after the single primary vaccination dose, and the dosing interval for a heterologous booster is the same as that authorized for a booster dose of the vaccine used for primary vaccination). Safety and effectiveness data supporting emergency use authorization of the Janssen COVID-19 Vaccine are detailed in the decision memorandum on the FDA website.

3.4 Therapies for COVID-19

The antiviral remdesivir is currently approved by the FDA for the treatment of COVID-19 in adults and pediatric patients (28 days of age and older and weighing at least 3 kg) with positive results of direct SARS-CoV-2 testing who are hospitalized, or who are not hospitalized and have mild-to-moderate COVID-19 and are at high risk for severe COVID-19. Additionally, the immune modulator baricitinib is approved by the FDA for the treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

Other pharmacological products for pre-exposure prophylaxis of COVID-19, post-exposure prophylaxis and/or treatment of COVID-19 that have received emergency use authorization are as follows:

Antivirals: Paxlovid (nirmatrelvir tablets and ritonavir tablets, co-packaged for oral use) is authorized under EUA for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Molnupiravir is authorized under EUA for the treatment of mild-to-

moderate COVID-19 in adults with positive results of direct SARS-CoV-2 testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options authorized by the FDA are not accessible or clinically appropriate.

SARS-CoV-2-targeting monoclonal antibodies: Bebtelovimab is authorized under EUA for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients 12 years of age and older weighing at least 40 kg with positive results of direct SARS-CoV-2 testing, who are at high risk for progression to severe COVID-19 and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate. Tixagevimab co-packaged with cilgavimab is authorized under EUA as pre-exposure prophylaxis for prevention of COVID-19 in certain adults and pediatric individuals (12 years of age and older weighing at least 40 kg).

Immune modulators: Baricitinib is authorized for the treatment of COVID-19 in hospitalized patients 2 to less than 18 years of age who require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO. Tocilizumab is authorized for the treatment of COVID-19 in hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.

COVID-19 convalescent plasma with high antibody titer is authorized for emergency use as a treatment for patients with COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment, in inpatient or outpatient settings.

4. EUA Amendment Request for the Novavax COVID-19 Vaccine for Use in Adolescents 12-17 Years of Age

On July 22, 2022, Novavax, Inc. submitted a request to amend the EUA for the two-dose primary series of Novavax COVID-19 Vaccine, Adjuvanted (also referred as NVX-CoV2373), to include use in individuals 12-17 years of age. This request is supported by clinical data from the adolescent expansion portion of Study 2019nCoV-301 as follows:

Safety data:

- Pre-crossover period: 1,487 NVX-CoV2373 recipients and 745 placebo recipients, of whom 84% had at least 2 months of follow-up. October 6, 2021 data extraction date.
- Post-crossover period: 665 NVX-CoV2373 crossover recipients and 1,353 placebo crossover recipients, of whom 40% had 1 to <2 months of follow-up. October 6, 2021 data extraction date.
- Supportive safety data (MAAEs, SAEs, and AESIs in a DSMB safety report) from the clinical database as of March 17, 2022.

Effectiveness data:

- Formal immunobridging comparisons between SARS-CoV-2 neutralizing antibody responses measured at Day 35 (14 days after the second dose of the initial vaccination series), including geometric mean titer (GMT) and seroconversion rate (SCR, defined as percentage of participants with a $\geqslant$4-fold difference in neutralizing antibody titers between Day 35 and Day 0) in participants 12-17 years of age (n=390) versus participants 18-25 years of age (n=415) in the same study.

- Efficacy against COVID-19 was assessed descriptively.

5. EUA Requirements, Guidance, and Considerations Pertaining to COVID-19 Vaccines

5.1 US Requirements to Support Issuance of an EUA for a Biological Product

Based on the declaration by the Secretary of the US Department of Health and Human Services (HHS) that the COVID-19 pandemic constitutes a public health emergency with a significant potential to affect national security or the health and security of United States citizens living abroad, FDA may issue an EUA after determining that certain statutory requirements are met (Section 564 of the FD&C Act (21 U.S.C. 360bbb-3)).

1. The chemical, biological, radiological, or nuclear agent referred to in the March 27, 2020, EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
2. Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective to prevent, diagnose, or treat such serious or life-threatening disease or condition that can be caused by SARS-CoV-2, or to mitigate a serious or life-threatening disease or condition caused by an FDA-regulated product used to diagnose, treat, or prevent a disease or condition caused by SARS-CoV-2.
3. The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product.
4. There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

If these criteria are met, under an EUA, FDA can authorize unapproved medical products (or unapproved uses of approved medical products) to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by threat agents.

5.2 Regulatory Considerations for Clinical Development of COVID-19 Vaccines in Children

The Vaccines and Related Biological Products Advisory Committee (VRBPAC) convened on June 10, 2021, to discuss, in general, the data needed to support authorization and/or licensure of COVID-19 vaccines for use in pediatric populations.

Effectiveness Data

Regulatory precedent with other preventive vaccines provides a basis for inference of vaccine effectiveness in pediatric populations based on immunobridging to an adult population in which clinical disease endpoint VE has been demonstrated for the same prototype vaccine. The immune marker(s) used for immunobridging do not need to be scientifically established to predict protection but should be clinically relevant to the disease. Based on available data in humans and animal models, FDA considers neutralizing antibody titers (a functional measure of the vaccine immune response against SARS-CoV-2) to be clinically relevant for immunobridging to infer effectiveness of COVID-19 vaccines in pediatric age groups. Because no specific neutralizing antibody titer has been established to predict protection against COVID-19, two immunogenicity endpoints (GMT and seroresponse rate) are considered appropriate for

comparing the range of neutralizing antibody responses elicited by the vaccine in pediatric versus young adult populations.

Safety Data

The size of the safety database sufficient to assess risks of COVID-19 vaccines for EUA in pediatric age groups would generally be the same as for other preventive vaccines for infectious diseases, provided that no specific safety concern is identified that could reasonably be evaluated in pre-authorization clinical trials. Safety data would include characterization of common adverse reactions (reactogenicity, including injection site and systemic adverse reactions), and less common but medically important adverse reactions. Data from Phase 3 studies should include a median follow-up duration of at least two months after completion of the full vaccination regimen to provide adequate information to assess a vaccine's benefit-risk profile. From a safety perspective, a 2-month median follow-up following completion of the full vaccination regimen will allow identification of potential adverse events that were not apparent in the immediate postvaccination period.

Depending on prior experience with the vaccine in adults, and prior experience with licensed vaccines based on the same or similar platforms, FDA has accepted an overall pediatric safety database in the range of ~500 to ~3,000 trial participants exposed to the age-appropriate dose and regimen intended for licensure. A control group (ideally placebo control) would be important to inform interpretation of safety data and to comply with the expectation for adequate and well-controlled studies to support licensure.

Post-licensure/post-authorization safety surveillance and observational studies in pediatric populations would be needed to evaluate for adverse reactions that occur too rarely to be detected in clinical trials.

6. FDA Review of Clinical Safety and Effectiveness Data

6.1 Overview of Clinical Studies

This EUA amendment request included data from the ongoing clinical study summarized in Table 1.

Table 1. Clinical Trial Considered in Support of Safety and Effectiveness of Novavax COVID-19 Vaccine Primary Series in Participants 12-17 Years of Age

Study Number/ Country	Description	NVX-CoV2373[1] N[2,3]	Placebo Comparator N[2]	Study Status
2019nCoV-301 Adolescent Expansion USA (Study 301)	Phase 3, randomized, observer-blinded, placebo-controlled study to evaluate the safety, efficacy, and immunogenicity of NVX-CoV2373 vaccine	1487	745	Ongoing

Source: adapted from EUA 28237, Amendments 3 and 58.
Abbreviations: COVID-19=coronavirus disease 2019; rS=recombinant sp ke
1. 5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant.
2. N: total number of participants in the Safety Analysis Set in the pre-crossover period (from randomization to the time of cross-over).
3. NVX-CoV2373 vaccine was manufactured at Par Sterile Products, LLC.

6.2 Study 2019nCoV-301 Adolescent Expansion

6.2.1 Design

The adolescent expansion portion of study 2019nCoV-301 (referred to hereafter as Study 301) is an ongoing randomized, observer-blind, placebo-controlled study to evaluate the efficacy, safety, and immunogenicity of NVX-CoV2373 in adolescents 12-17 years of age. Approximately 3,000 adolescents were planned to be enrolled exclusively from US study sites and randomized in a 2:1 ratio via block randomization to receive 2 intramuscular injections of NVX-CoV2373 or placebo (normal saline) administered 3 weeks apart. There was no pre-randomization stratification by demographics, but clinical sites were instructed to balance recruitment with respect to the two age subgroups (12 through 14 years of age and 15 through 17 years of age [abbreviated 12-14 and 15-17 years of age, respectively]) and to strive for a diverse population including underserved minorities. A data monitoring committee (DMC) reviewed safety data (i.e., 7 days of reactogenicity and general safety profile following each dose) from a sentinel group of approximately 60 adolescents to allow continued enrollment and administration of Dose 1 and Dose 2.

The adolescent expansion was initiated on April 26, 2021 (first sentinel participant screened). Adolescent participants 12-17 years of age at screening were enrolled, including those with clinically stable chronic conditions (such as well-controlled human immunodeficiency virus infection) who had no previous history of laboratory confirmed SARS-CoV-2 infection or COVID-19 prior to randomization. Participants with immunodeficiency conditions, receipt of immunosuppressive therapy, immunoglobulin, or blood derived products within 90 days, who were pregnant or breastfeeding, or who were first-degree relatives of any study team members were excluded. After review of the sentinel cohort safety data on May 6, 2021, broader enrollment at all 73 clinical study sites across the US began. Due to the availability of COVID-19 vaccines authorized for EUA to adolescents 16 to < 18 years of age, the study plan was modified after the EUA-required safety data had been accrued (median duration of 2 months safety follow-up after the second vaccination) to offer the alternative vaccine/placebo in a blinded fashion (“blinded crossover”). Enrollment concluded on June 5, 2021, after enrollment of approximately 2,200 adolescents, due to slowed enrollment and the need to ensure a median duration of 2 months of safety follow up prior to implementation of the blinded crossover period ahead of the beginning of the school year in September. At the time of the August 9, 2021 data cutoff, the Delta (B.1.617.2 and AY lineages) variant was the predominant VOC circulating in the US.

Blood samples for serologic assessments were collected from all adolescent participants before Dose 1, 30 days after Dose 2, and at selected subsequent time points thereafter, including immediately prior to the crossover vaccination. Anti-NP antibodies were assessed via the Roche Elecsys Anti-SARS-CoV-2 assay. Wild-type virus microneutralization was evaluated with a validated assay.

Symptoms of COVID-19 experienced by participants during post-vaccination follow-up prompted an unscheduled illness visit and nasopharyngeal swab. Molecular confirmation of SARS-CoV-2 infection [using the Abbott Real Time SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) assay] by the central laboratory was required to meet the primary and secondary efficacy endpoint case definitions.

Primary Immunogenicity Evaluation

Vaccine effectiveness in adolescents 12-17 years of age was inferred based on a comparison of neutralizing antibody response at Day 35 (pre-crossover period) in adolescent participants to that observed in participants 18-25 years of age ('adult main study') who were also enrolled in study 301.

The primary immunogenicity endpoint is SARS-CoV-2 neutralizing antibody response against the reference strain (SARS-CoV-2 hCoV-19/Australia/VIC01/2020) at Day 35 (i.e., 14 days after the second dose of the initial vaccination series), measured by geometric mean titer (GMT) and seroconversion rate (SCR, defined as the percentage of participants with a ≥4-fold difference in neutralizing antibody titers between Day 35 and Day 0), using a microneutralization assay.

Statistical immunobridging success criteria included the following:

- Point estimate of the GMR ($GMT_{18\text{-}25YO}$ /$GMT_{12\text{-}17YO}$) ≥0.82
- Lower limit of the two-sided 95% CI of the GMR >0.67
- Lower limit of the 95% CI of the difference in SCRs ($SCR_{18\text{-}25YO}$-$SCR_{12\text{-}17YO}$) >−10%.

The primary immunogenicity endpoint was assessed based on the PP-IMM (Day 35) population of the adolescent expansion and the adult main study. The PP-IMM (Day 35) analysis set included participants who were seronegative to anti-SARS-CoV-2 nucleoprotein (NP) antibodies and PCR-negative at baseline, with at least a baseline and Day 35 serum sample result available and had no major protocol violations that were considered clinically relevant to impact immunological measures at the specified timepoint. A total of 750 adolescent participants 12-17 years of age and 750 adult participants 18-25 years of age were randomly selected from the adolescent expansion and the adult main study, respectively, to provide approximately 400 participants in each age cohort for testing of neutralizing antibody titers (accounting for the 2:1 randomization and 20% non-evaluable rate).

To facilitate cross-product comparisons, Novavax revised the presentation of the immunogenicity data by inverting the ratios from adults versus adolescents to adolescents versus adults for alignment with immunogenicity analyses performed for other COVID-19 vaccines.

Efficacy Evaluation

Descriptive analyses were performed to evaluate the efficacy of a two-dose regimen (administered at Days 0 and 21) of NVX-CoV2373 compared to placebo against PCR-confirmed symptomatic COVID-19 illness diagnosed ≥7 days after completion of the second injection. The primary efficacy endpoint is the first episode of PCR-confirmed symptomatic mild, moderate, or severe COVID-19 with onset ≥7 days after the second dose in adolescent participants seronegative at baseline. COVID-19 case definitions are presented in Table 2. The primary efficacy endpoint was assessed based on data collected in the pre-crossover period (i.e., until a participant received the first blinded crossover vaccination or until the efficacy data cutoff of August 9, 2021, whichever came first).

VE was defined as 1 minus the ratio of incidence rates (RR) between the NVX-CoV2373 and placebo groups. The RR was estimated by exponentiating the treatment group coefficient from a Poisson regression analysis with robust error variance. To assess incident rates rather than absolute counts of cases accounting for differences in follow-up times among participants, an

offset was utilized in the Poisson regression. A 2-sided 95% CI was constructed around the estimate.

Table 2. COVID-19 Case Definitions

Severity	Case Definition
Mild	• Fever (defined by subjective or objective measure, regardless of use of anti-pyretic medications) • New onset cough OR ≥2 additional COVID-19 symptoms: • New onset or worsening of shortness of breath or difficulty breathing compared to baseline • New onset fatigue • New onset generalized muscle or body aches • New onset headache • New loss of taste or smell • Acute onset of sore throat, congestion, and runny nose • New onset nausea, vomiting, or diarrhea

Moderate	• High fever (≥38.4°C) for ≥3 days (regardless of use of anti-pyretic medications, need not be contiguous days)
	• Any evidence of significant LRTI:
	  • Shortness of breath (or breathlessness or difficulty breathing) with or without exertion (greater than baseline)
	  • Tachypnea: 24 to 29 breaths per minute at rest
	  • SpO_2: 94% to 95% on room air
	  • Abnormal chest X-ray or chest computerized tomography consistent with pneumonia or LRTI
	  • Adventitious sounds on lung auscultation crackles/rales, wheeze, rhonchi, pleural rub, stridor)

Severe	• Tachypnea: ≥30 breaths per minute at rest
	• Resting heart rate ≥125 beats per minute
	• Oxygen saturation ≤93% on room air or ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen <300 mm Hg
	• High flow oxygen therapy or non-invasive ventilation/non-invasive positive pressure ventilation (e.g., continuous positive airway pressure or bilevel positive airway pressure)
	• Mechanical ventilation or extracorporeal membrane oxygenation
	• One or more major organ system dysfunction or failure (e.g., cardiac/circulatory, pulmonary, renal, hepatic, and/or neurological, to be defined by diagnostic testing/clinical syndrome/interventions), including any of the following:
	  • Acute respiratory distress syndrome
	  • Acute renal failure
	  • Acute hepatic failure
	  • Acute right or left heart failure
	  • Septic or cardiogenic shock (with shock defined as systolic blood pressure <90 mm Hg OR diastolic blood pressure <60 mm Hg)
	  • Acute stroke (ischemic or hemorrhagic)
	  • Acute thrombotic event: acute myocardial infarction, deep vein thrombosis, pulmonary embolism
	  • Requirement for: vasopressors, systemic corticosteroids, or hemodialysis.
	  • Admission to an intensive care unit
	  • Death

Source: Study 301, version 9.0, dated May 14, 2021.
Abbreviations: COVID-19=coronavirus disease-2019; LRTI=lower respiratory tract infection

Study participants and parent(s)/caregiver(s) were provided paper memory aids with a list of symptoms suggestive of COVID-19 and instructed to notify the study site as soon as possible or during the remote follow-up assessments if they experienced symptoms beginning on Day 4 through the first 12 months of the study. Acute illness visits were scheduled if the symptoms were judged to warrant a focused physical exam, nasal swab, and a blood sample. Unlike adults in the main study, adolescent participants were not required to complete the InFLUenza Patient-Reported Outcome (FLU-PRO) instrument or self-swabbing.

All cases meeting the severe/critical criteria were to be adjudicated by a blinded clinical severity adjudication committee to confirm severity.

Select Secondary Objectives

- To evaluate the efficacy of a 2-dose regimen against PCR-confirmed symptomatic COVID-19 illness due to a SARS-CoV-2 variant not considered as a "variant of concern/interest" (VOC/VOI) according to the CDC Variants Classification, diagnosed ⩾7 days after completion of the second injection in the initial set of vaccinations of adolescent participants 12-17 years of age
- To assess the neutralizing antibody response to SARS-CoV-2 for adolescent participants by subsets with and without anti-NP antibodies at baseline, compared with that observed in adult participants 18-25 years of age from the adult main study (Per-Protocol Immunogenicity set) in the pre-crossover period

Exploratory Efficacy Objective

- To evaluate the efficacy of the vaccine compared to placebo against PCR-confirmed symptomatic COVID-19 illness diagnosed ≥7 days after completion of the 2-dose regimen that is demonstrated to be due to a SARS-CoV2 variant shown by gene sequencing to represent a "variant of concern/interest" according to the CDC Variants Classification

Evaluation of Safety

Safety follow-up evaluations are planned through 24 months post-last dose of the primary series. Safety assessments include the following:

- Solicited local (pain, tenderness, erythema, and swelling/induration) and systemic (fever, malaise, fatigue, arthralgia, myalgia, headache, nausea/vomiting) ARs during the 7 days following vaccination, pre-crossover (also described as reactogenicity symptoms)
- Unsolicited AEs, both pre- and post-crossover, from Dose 1 through 28 days post Dose 2; participants who only received the first dose in the pre- and post-crossover periods were monitored for non-serious unsolicited adverse events through 49 days after administration of vaccine or placebo
- MAAEs, both pre- and post-crossover, from Dose 1 through 28 days post Dose 2; participants who only received the first dose in the pre- and post-crossover periods were monitored for non-serious unsolicited adverse events through 49 days after administration of vaccine or placebo or if only Dose 1 is provided then 49 days after Dose 1
- MAAEs attributed to study vaccine, SAEs, and AESIs (defined as COVID-related AEs and PIMMCs), both pre- and post-crossover, for the duration of the study in all participants
- Vital sign measurements at specified clinic visits in all participants
- Physical examination findings at specified clinic visits in all participants
- Pregnancy and accompanying outcomes in all participants

The Data Safety Monitoring Committee, consisting of external experts, monitored safety and advised the Sponsor at scheduled and *ad hoc* meetings. An unblinded statistician monitored data for the pre-specified stopping boundary, which would indicate that the vaccine causes harm by increasing the rate of mild, moderate or severe COVID-19.

Datasets Reviewed

The immunogenicity, efficacy, and safety analyses are based on the adolescent data extracted on October 6, 2021 (referred to as October 6, 2021 extraction hereafter). The October 6, 2021 extraction included data that were fully cleaned up to August 9, 2021 (referred to as August 9, 2021 cutoff hereafter). The immunogenicity and efficacy analyses were performed based on the fully cleaned data through the August 9, 2021 cutoff. Because the "blinded crossover" was initiated around August 9, 2021, in order to evaluate any additional safety data accrued post-crossover, the safety analyses were performed based on all available data from the October 6, 2021 extraction including potentially uncleaned data from August 9, 2021 to October 6, 2021. The analysis sets are defined in Table 3.

The immunobridging analyses involving adult participants 18-25 years of age were performed based on the adult data with a September 27, 2021 cutoff.

Table 3. Analysis Sets

Population	Description
Full Analysis Set (FAS)	Participants who were randomized and received at least 1 dose of study vaccine/placebo, regardless of protocol violations or missing data.
Per-Protocol Efficacy	Participants who were randomized, received both doses as assigned, had no immunologic or virologic evidence of prior COVID-19 at the time of vaccination, and no major protocol deviations that would impact the efficacy outcomes (e.g., baseline seropositivity for anti-SARS-CoV-2 nucleoprotein, baseline positivity for SARS-CoV-2 RNA RT-PCR from nasal swab, COVID-19 event at any time before 7 days after the second injection, participants were censored at the time of protocol deviation).
Per-Protocol Efficacy Set 2	Participants with the same eligibility as the Per-Protocol Efficacy set, with the exception of baseline COVID-19 serostatus positive at time of enrollment.
Per-Protocol Immunogenicity (Day 35)	Participants that have at least a baseline and 1 serum sample result available after vaccination and have no major protocol violations that would impact immunological measures at the specified timepoint, excluding participants who had a PCR-positive nasal swab between baseline up to the visit analyzed.
Per Protocol Immunogenicity- 2	Participants with the same eligibility as PP-IMM, and SARS-CoV-2-exposed participants at baseline (pre-Dose 1) determined by nasal swab or seropositivity at screening.
Safety	Participants who were randomized and received at least 1 dose of study vaccine/placebo. For participants who received both active and placebo vaccine during the initial or crossover period, the participant was analyzed as part of the active group.

Source: Study 301 protocol version 9.0, dated May 14, 2021.
Abbreviations: SARS CoV-2=severe acute respiratory syndrome coronavirus; RT-PCR=reverse transcription polymerase chain reaction; COVID-19=coronavirus disease-2019.

6.2.2 Participant Disposition and Inclusion in Analysis Populations

A total of 2,304 adolescent participants were screened and 2.5% of those screened (n=57) did not proceed with randomization due to failure to meet all eligibility criteria (n=44; 1.9%), withdrawal by participant (n=11; 0.5%), failure to meet randomization criteria (n=1; <0.1%), or other (n=1; <0.1%).

All 2,247 randomized adolescents were included in the ITT analysis set. Of the randomized adolescents 2,232 (99.3%) were included in the Full Analysis Set (FAS), 1,799 (80.1%) were included in the Per-Protocol Efficacy (PP-EFF) Analysis Set, and 1,654 (73.6%) were included in the Per-Protocol Immunogenicity (PP-IMM) Analysis Set. See Table 3 for the definitions of the analysis sets.

Table 4 describes the disposition of participants among all randomized. Rates of discontinuation were similar in the active (5.2%) and placebo (7.1%) arms. There were no major differences between the two treatment arms with respect to discontinuation. The most common reason was withdrawal by the participant for reasons unrelated to COVID-19 (3.6% and 5.2% respectively) Table 5.

Table 4. Disposition, All Randomized Participants, Study 301 Adolescent Expansion, October 6, 2021 Extraction Date

Parameter	NVX-CoV2373 n (%)	Placebo n (%)	Total n (%)
Randomized	1491	756	2247
Treated	1487	745	2232
Blinded, placebo-controlled follow-up period	--	--	--
Completed only 1 dose	19 (1.3)	15 (2.0)	34 (1.5)
Completed 2 doses	1468 (98.7)	730 (98.0)	2198 (98.5)
Discontinued from original blinded placebo-controlled vaccination period	77 (5.2)	54 (7.1)	131 (5.8)
Reason for discontinuation	--	--	--
Withdrawal by subject	53 (3.6)	39 (5.2)	92 (4.1)
Lost to follow-up	18 (1.2)	10 (1.3)	28 (1.2)
Other	6 (0.4)	5 (0.7)	11 (0.5)
Adverse event	0	0	0
Death	0	0	0

Source: EUA 28237 Amendment 30, Table 1.
Note: Denominators are based on the number of treated participants.

Table 5 describes the analysis populations and the reasons for exclusion from each. Of the participants randomized to a study arm (ITT set), a total of 7 participants in NVX-CoV2373 arm (0.5%) and 8 participants in the placebo arm (1.1%) were not dosed and were excluded from the FAS set. Positive anti-NP serostatus at baseline was the most common reason for NVX-CoV2372 and placebo recipients to be excluded from the PP-EFF set (15.2% and 16.0%, respectively). SARS-CoV-2 exposure at baseline was the most common reason for NVX-CoV2372 and placebo recipients to be excluded from the PP-IMM set (14.1% and 14.6%, respectively). The most apparent imbalance across treatment arms in reason for exclusion was protocol deviation, which occurred in 0.6% of NVX-CoV2373 recipients compared to 1.5% of placebo recipients. It is unlikely that this imbalance, which may be attributable to relatively small sample sizes and the 2:1 randomization scheme, impacted effectiveness analyses.

Table 5. Analysis Populations, All Randomized Subjects, Study 301 Adolescent Expansion,

Population	NVX-CoV2373 n (%)	Placebo n (%)	Total n (%)
ITT Set[1,2]	1491 (100)	756 (100)	2247 (100)
Excluded from all Analysis Sets	7 (0.5)	8 (1.1)	15 (0.7)
Not dosed	7 (0.5)	8 (1.1)	15 (0.7)

Population	NVX-CoV2373 n (%)	Placebo n (%)	Total n (%)
FAS Set[3,4]	1484 (99.5)	748 (98.9)	2232 (99.3)
PP-EFF[5,6]	1205 (80.8)	594 (78.6)	1799 (80.1)
Excluded from PP-EFF	286 (19.2)	162 (21.4)	448 (19.9)
Reason for exclusion	--	--	--
Baseline positive anti-NP result	227 (15.2)	121 (16.0)	348 (15.5)
Censored prior to observation period	30 (2.0)	20 (2.6)	50 (2.2)
Unblinded	19 (1.3)	8 (1.1)	27 (1.2)
Protocol deviation	9 (0.6)	11 (1.5)	20 (0.9)
Withdrawal from Study	2 (0.1)	2 (0.3)	4 (0.2)
Did not complete vaccination schedule	26 (1.7)	23 (3.0)	49 (2.2)
Baseline positive PCR result	12 (0.8)	9 (1.2)	21 (0.9)
PP-EFF-2[6,7]	1423 (95.4)	704 (93.1)	2127 (94.7)
Excluded from PP-EFF-2	68 (4.6)	52 (6.9)	120 (5.3)
Reason for exclusion	--	--	--
Censored prior to observation period	30 (2.0)	20 (2.6)	50 (2.2)
Unblinded	19 (1.3)	8 (1.1)	27 (1.2)
Protocol deviation	9 (0.6)	11 (1.5)	20 (0.9)
Withdrawal from study	2 (0.1)	2 (0.3)	4 (0.2)
Did not complete vaccination schedule	26 (1.7)	23 (3.0)	49 (2.2)
Baseline positive PCR result	12 (0.8)	9 (1.2)	21 (0.9)
PP-IMM (Day 35)[6,8]	1120 (75.1)	534 (70.6)	1654 (73.6)
Excluded from PP-IMM	371 (25.0)	222 (29.4)	593 (26.4)
Reason for exclusion	--	--	--
SARS-CoV-2 exposure at baseline	210 (14.1)	110 (14.6)	320 (14.2)
Did not complete vaccination schedule	26 (1.7)	23 (3.0)	49 (2.2)
Randomized but never dosed	7 (0.5)	8 (1.1)	15 (0.7)
Sample not collected	85 (5.7)	63 (8.3)	148 (6.6)
Infection prior to visit	7 (0.5)	6 (0.8)	13 (0.6)
Protocol deviation	69 (4.6)	43 (5.7)	112 (5.0)

Population	NVX-CoV2373 n (%)	Placebo n (%)	Total n (%)
PP-IMM-2 (Day 35)[6,9]	1330 (89.2)	644 (85.2)	1974 (87.9)
Excluded from PP-IMM-2	161 (10.8)	112 (14.8)	273 (12.1)
Reason for exclusion	--	--	--
Did not complete vaccination schedule	26 (1.7)	23 (3.0)	49 (2.2)
Randomized but never dosed	7 (0.5)	8 (1.1)	15 (0.7)
Sample not collected	85 (5.7)	63 (8.3)	148 (6.6)
Infection prior to visit	7 (0.5)	6 (0.8)	13 (0.6)
Protocol deviation	69 (4.6)	43 (5.7)	112 (5.0)

Source: IND 22430 Amendment 322, Table 8.
Abbreviations: FAS=Full Analysis Set; ITT=Intent-to-Treat; NP=nucleocapsid protein; PCR=polymerase chain reaction; PP-EFF=Per-Protocol Efficacy Analysis Set; PP-IMM=Per-Protocol Immunogenicity; PP-IMM-2=Per-Protocol Immunogenicity 2
1. ITT Analysis Set included all participants randomized into the study.
2. Percentages were calculated based on randomized participants.
3. FAS included all participants randomized who received at least 1 dose of study vaccine/placebo and tabulated with randomized treatment.
4. Percentages were calculated based on randomized (ITT Analysis Set) in each column.
5. PP-EFF Analysis Set included all participants who received the full prescr bed regimen of study vaccine/ placebo, had no major protocol deviations prior to first COVID-19 positive episode or administrative censoring, with no confirmed infection or prior infection due to SARS-CoV-2 at baseline and not censored prior to the start of the observation period.
6. Percentages were calculated based on the FAS in each column.
7. PP-EFF-2 Analysis Set followed the same method described in the PP-EFF Analysis Set except that it included all participants regardless of baseline SARS-CoV-2 serostatus.
8. PP-IMM Analysis Set included all participants who have at least a baseline and 1 serum sample result available after vaccination and have no major protocol violations that would impact immunological measures at the specified timepoint.
9. PP-IMM-2 Analysis Set followed the same method descr bed in the PP-IMM Analysis Set except that it included all participants regardless of baseline SARS-CoV-2 serostatus.
Note: Participants may be excluded for more than 1 reason.

6.2.3 Demographics and Other Baseline Characteristics

Table 6 describes the demographics and other baseline characteristics for the Safety Analysis Set, Per-Protocol Efficacy Analysis Set (PP-EFF), and Per-Protocol Immunogenicity Analysis Set. There were no notable imbalances. The median age of participants in all analysis sets was 14 years old. Representation of age subgroups, sex, and race were similar across the analysis groups. Median weight across analysis sets was approximately 60 kg (ranging between 58.7 to 61.7 kg). Approximately 25% of participants were classified as obese

Table 6. Demographics and Other Baseline Characteristics for Safety Analysis Set, Per-Protocol Efficacy Analysis Set (PP-EFF), and Per-Protocol Immunogenicity Analysis Set (Day 35) [PP-IMM (Day 35)]

Parameter	Safety Analysis Set NVX-CoV2373 N=1487	Safety Analysis Set Placebo N=745	PP-EFF NVX-CoV2373 N=1205	PP-EFF Placebo N=594	PP-IMM (Day 35) NVX-CoV2373 N=1120	PP-IMM (Day 35) Placebo N=534
Age, years	--	--	--	--	--	--
Mean (SD)	13.9 (1.4)	13.8 (1.4)	13.8 (1.39)	13.8 (1.41)	13.8 (1.39)	13.7 (1.42)
Median	14.0	14.0	14.0	14.0	14.0	14.0
Minimum, maximum	12, 17	12, 17	12, 17	12, 17	12, 17	12, 17
Age subgroup, n (%)	--	--	--	--	--	--
12-14 years	998 (67.1)	500 (67.1)	822 (68.2)	407 (68.5)	763 (68.1)	366 (68.5)
15-17 years	489 (32.9)	245 (32.9)	383 (31.8)	187 (31.5)	357 (31.9)	168 (31.5)
Sex, n (%)	--	--	--	--	--	--
Male	756 (50.8)	416 (55.8)	622 (51.6)	328 (55.2)	579 (51.7)	295 (55.2)
Female	731 (49.2)	329 (44.2)	583 (48.4)	266 (44.8)	541 (48.3)	239 (44.8)
Race, n (%)	--	--	--	--	--	--
White	1115 (75.0)	545 (73.2)	922 (76.5)	447 (75.3)	863 (77.1)	401 (75.1)
Black or African American	202 (13.6)	108 (14.5)	155 (12.9)	77 (13.0)	139 (12.4)	67 (12.5)
American Indian or Alaska Native	32 (2.2)	14 (1.9)	13 (1.1)	6 (1.0)	13 (1.2)	6 (1.1)
Asian	43 (2.9)	34 (4.6)	38 (3.2)	26 (4.4)	34 (3.0)	23 (4.3)
Mixed origin	82 (5.5)	37 (5.0)	67 (5.6)	33 (5.6)	63 (5.6)	33 (6.2)
Native Hawaiian or other Pacific Islander	3 (0.2)	2 (0.3)	3 (0.2)	1 (0.2)	3 (0.3)	1 (0.2)
Not reported	10 (0.7)	5 (0.7)	7 (0.6)	4 (0.7)	5 (0.4)	3 (0.6)
Ethnicity, n (%)	--	--	--	--	--	--
Not Hispanic or Latino	1208 (81.2)	607 (81.5)	1015 (84.2)	494 (83.2)	943 (84.2)	449 (84.1)
Hispanic or Latino	274 (18.4)	138 (18.5)	185 (15.4)	100 (16.8)	173 (15.4)	85 (15.9)
Not reported	2 (0.1)	0	2 (0.2)	0	1 (<0.1)	0
Unknown	3 (0.2)	0	3 (0.2)	0	3 (0.3)	0
Weight, kg	--	--	--	--	--	--
Mean (SD)	66.5 (21.82)	64.8 (21.23)	65.8 (21.25)	63.5 (20.26)	65.8 (20.89)	63.9 (20.51)
Median	61.7	59.9	61.3	58.7	61.3	58.8
Minimum, maximum	29.4, 198.6	26.0, 173.8	30.3, 158.3	26.0, 173.8	30.3, 154.2	26.0, 173.8

Parameter	Safety Analysis Set NVX-CoV2373 N=1487	Safety Analysis Set Placebo N=745	PP-EFF NVX-CoV2373 N=1205	PP-EFF Placebo N=594	PP-IMM (Day 35) NVX-CoV2373 N=1120	PP-IMM (Day 35) Placebo N=534
BMI, kg/m^2	--	--	--	--	--	--
Mean (SD)	24.3 (6.92)	23.7 (6.76)	24.0 (6.71)	23.3 (6.58)	24.0 (6.66)	23.5 (6.68)
Median	22.6	21.9	22.5	21.6	22.5	21.8
Minimum, maximum	14.0, 59.4	10.0, 63.8	14.0, 53.0	10.0, 63.8	14.0, 53.0	10.0, 63.8
BMI category, n (%)	--	--	--	--	--	--
Underweight (<18.0 kg/m^2)	40 (2.7)	28 (3.8)	35 (2.9)	26 (4.4)	31 (2.8)	23 (4.3)
Normal (18.0 to 24.9 kg/m^2)	771 (51.8)	417 (56.0)	632 (52.4)	342 (57.6)	588 (52.5)	302 (56.6)
Overweight (25.0 to 29.9 kg/m^2)	270 (18.2)	107 (14.4)	224 (18.6)	84 (14.1)	212 (18.9)	77 (14.4)
Obese (≥30.0 kg/m^2)	406 (27.3)	193 (25.9)	314 (26.1)	142 (23.9)	289 (25.8)	132 (24.7)
Height, cm	--	--	--	--	--	--
Mean (SD)	164.9 (10.34)	164.7 (10.36)	164.8 (10.35)	164.4 (10.28)	164.9 (10.35)	164.4 (10.38)
Median	165.0	164.3	165.0	164.0	165.0	163.8
Minimum, maximum	98.6, 195.6	124.5, 201.4	98.6, 195.6	124.5, 193.0	98.6, 195.6	124.5, 193.0
SARS-CoV-2 serostatus, n (%)	--	--	--	--	--	--
Anti-NP	--	--	--	--	--	--
Positive	227 (15.3)	121 (16.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Negative	1254 (84.3)	623 (83.6)	1199 (99.5)	593 (99.8)	1115 (99.6)	533 (99.8)
Missing	6 (0.4)	1 (0.1)	6 (0.5)	1 (0.2)	5 (0.4)	1 (0.2)
PCR, n(%)	--	--	--	--	--	--
Positive	12 (0.8)	9 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Negative	1473 (99.1)	736 (98.8)	1203 (99.8)	594 (100)	1119 (99.9)	534 (100)
Missing	2 (0.1)	0 (0.0)	2 (0.2)	0 (0.0)	1 (<0.1)	0 (0.0)
Anti-NP/PCR	--	--	--	--	--	--
Positive	234 (15.7)	125 (16.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Negative	1252 (84.2)	620 (83.2)	1204 (99.9)	594 (100)	1120 (100)	534 (100)
Missing	1 (<0.1)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Adapted from IND22430 Amendment 322, Tables 11-13.
Abbreviations: BMI=body mass index; NP=nucleocapsid protein; PCR=polymerase chain reaction; SD=standard deviation; N=number of participants in cohort; n=number of participants with indicated characteristic.

Table 7 describes the demographics and other baseline characteristics for the population included in the primary immunobridging analysis. Both the adolescent (median age 14 years old) and adult (median age 22 years old) populations had proportionate representation of males and females, with the majority identifying as White (79.2% and 69.6%, respectively), followed by Black or African American (11.5% and 10.4%, respectively), and Non-Hispanic or Latino (83.3% and 67.2%, respectively). With respect to BMI, approximately 50% of participants in both age cohorts were overweight (18.5% and 27.7%, respectively) or obese (24.9% and 23.6%, respectively).

Table 7. Demographics and Other Baseline Characteristics for Adolescent and Adult Participants Included in the Immunobridging Analyses, Per Protocol Immunogenicity Analysis Set

Parameter	NVX-CoV2373 Adolescent Participants 12-17 Years of Age N=390	NVX-CoV2373 Adult Participants 18-25 Years of Age N=415
Age, years	--	--
Mean (SD)	13.7 (1.3)	21.9 (2.28)
Median	14	22
Minimum, maximum	12, 17	18, 25
Sex, n (%)	--	--
Male	204 (52.3)	194 (46.7)
Female	186 (47.7)	221 (53.3)
Race, n (%)	--	--
White	309 (79.2)	289 (69.6)
Black or African American	45 (11.5)	43 (10.4)
American Indian or Alaska Native	5 (1.3)	37 (8.9)
Asian	10 (2.6)	30 (7.2)
Mixed origin	20 (5.1)	7 (1.7)
Native Hawaiian or other Pacific Islander	0	2 (0.5)
Not reported	1 (0.3)	4 (1.4)
Missing	0	1 (0.2)
Ethnicity, n (%)	--	--
Not Hispanic or Latino	325 (83.3)	279 (67.2)
Hispanic or Latino	65 (16.7)	135 (32.5)
Missing	0 (0)	1 (0.2)
Weight, kg	--	--
Mean (SD)	65 (20.22)	78 (22.16)
Median	60.5	74.3
Minimum, maximum	32.1, 146	42, 204.5
BMI, kg/m^2	--	--
Mean (SD)	23.6 (6.31)	26.6 (6.84)
Median	22.1	25.1
Minimum, maximum	14.2, 53	16.4, 70.6
BMI category, n (%)	--	--
Underweight (<18.0 kg/m^2)	12 (3.1)	10 (2.4)
Normal (18.0 to 24.9 kg/m^2)	209 (53.6)	192 (46.3)
Overweight (25.0 to 29.9 kg/m^2)	72 (18.5)	115 (27.7)
Obese (≥30.0 kg/m^2)	97 (24.9)	98 (23.6)

Parameter	NVX-CoV2373 Adolescent Participants 12-17 Years of Age N=390	NVX-CoV2373 Adult Participants 18-25 Years of Age N=415
Height, cm	--	--
Mean (SD)	165.1 (9.61)	170.8 (10.39)
Median	165.1	170.2
Minimum, maximum	132.1, 193.4	139.2, 198.1

Source: FDA-generated table.
Abbreviations: BMI=body mass index; SD=standard deviation; N=number of participants in cohort; n=number of participants with indicated characteristic

6.2.4 Vaccine Effectiveness

6.2.4.1 Primary Immunogenicity Analyses

Vaccine effectiveness in adolescents 12-17 years of age was inferred based on comparisons of neutralizing antibody response at Day 35 (pre-crossover period) in adolescent participants to that observed in participants 18-25 years of age from the same study. Table 8 and Table 9 summarize the results of the primary immunobridging analyses. The point estimate of the ratio of GMTs in adolescents versus adults was 1.47 and the lower bound of the 95% CI was 1.26, both of which met the corresponding success criteria of ≥0.82 and >0.67. SCRs were similar in both age cohorts, and the lower bound of the 95% CI for difference in SCR among the adolescent cohort and the adult cohort was −2.75%, which met the corresponding success criterion of > −10%.

Table 8. Ratio of Geometric Mean Neutralizing Antibody Titers for SARS-CoV-2 Wild-Type Virus at Day 35 in Adolescent Participants Compared to Adult Participants, Per Protocol Immunogenicity Analysis Set

MN (1/Dilution)	NVX-CoV2373 Participants 12-17 Years N=390	NVX-CoV2373 Participants 18-25 Years N=415	Participants 12-17 Years vs 18-25 Years
Day 35 GMT	--	--	--
GMT	3859.60	2611.83	--
95% CI[1]	(3422.83, 4352.10)	(2367.38, 2881.52)	--
GMR[2]	--	--	1.47
95% CI	--	--	(1.26, 1.72)

Source: EUA 28237 Amendment 71, Table 14.2.7.2.1r.
Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; GMR=ratio of GMT, which is defined as the ratio of 2 GMTs for comparison of adolescents to adults; GMT=geometric mean titer; MN=microneutralization; N=number of participants in assay-specific PP-IMM Analysis Set for Study 301 (Adult main study portion) and for Adolescent Expansion
1. The 95% CI for GMT was calculated based on the t-distribution of the log-transformed values, then back transformed to the original scale for presentation.
2. An ANCOVA with age cohort as main effect and baseline MN Assay neutralizing antibodies as covariate was performed to estimate the GMT ratio in adolescents compared to adults. Individual response values recorded as below the LLOQ were set to half LLOQ.

Table 9. Ratio of Seroconversion Rate of MN Assay Neutralizing Antibody Titers for SARS-CoV-2 Wild-Type Virus at Day 35 in Adolescent Participants Compared to Adult Participants, Per Protocol Immunogenicity Analysis Set

MN (1/Dilution)	NVX-CoV2373 Participants 12-17 Years N=390	NVX-CoV2373 Participants 18-25 Years N=415	Participants 12-17 Years vs 18-25 Years
Day 35 SCR[1]	--	--	--
n	385	414	--
SCR	98.72%	99.76%	--
95% CI	(97.03%, 99.58%)	(98.66%, 99.99%)	--
SCR difference[2]	--	--	−1.04%
95% CI	--	--	-2.75%, 0.20%

Source: EUA 28237 Amendment 71, Table 14.2.7.2.1r.
Abbreviations: CI=confidence interval; MN=microneutralization; N=number of participants in assay-specific PP-IMM Analysis Set for Study 301 (Adult main study portion) and for Adolescent Expansion; SCR=seroconversion rate
1. SCR is defined as percentage of participants with a ≥4-fold difference in titers between Day 35 and Day 0. The n for SCR is the number of subjects who reported ≥4-fold increase in MN titer from Day 0.The 95% CI for SCR was calculated using the Clopper-Pearson exact method.
2. Difference in SCR in the adolescents minus that of those 18-25 years old. The 95% CI for the difference of SCR between groups was calculated with the method of Mietteinen and Nurminen.

6.2.4.2 Supportive Efficacy Analyses

The primary endpoint for this supportive analysis of vaccine efficacy was PCR-confirmed symptomatic mild, moderate, or severe COVID-19 occurring at least 7 days after the second dose of vaccine in adolescent participants who were serologically-negative and PCR-negative at baseline (PP-EFF set).

A total of 16 cases of PCR-confirmed symptomatic COVID-19 with onset from at least 7 days after second vaccination were accrued by August 9, 2021. Of the 16 cases, 5 occurred in the NVX-CoV2373 arm (median surveillance time of 60 days) and 11 occurred in the placebo arm (median surveillance time of 57 days). All 16 cases were mild in severity. Nine cases (2 NVX-CoV2373, 7 placebo) were due to Delta variant (B.1.617.2; AY.3); sequencing could not be completed for the other 7 cases due to low viral load.

As shown in Table 10, VE against COVID-19 with onset at least 7 days after the second dose was 78.3% (95% CI 37.6, 92.5).

Table 10. Vaccine Efficacy in Protecting Against PCR-Confirmed COVID-19 With Onset From 7 Days After Second Injection, Per-Protocol Efficacy Set

Age Group	NVX-CoV2373 Cases[1] n/N (%) (Mean Incidence Rate/ 100 Person-Years)	Placebo Cases[1] n/N (%) (Mean Incidence Rate/ 100 Person-Years)	Vaccine Efficacy[2] (95% CI)
All participants	5/1205 (0.4) (2.7)	11/594 (1.9) (12.4)	78.4 (37.6, 92.5)

Source: IND 22430 Amendment 322, adapted from Table 14.
Abbreviations: CI=confidence interval; COVID-19=coronavirus disease-2019; NP=nucleocapsid protein; PCR=polymerase chain reaction; RR=ratio of incidence rate.
N=number of participants in Per-Protocol Efficacy Set; n=number of cases[1]
1. Case defined as first occurrence of PCR-confirmed mild, moderate or severe COVID-19 disease with onset from 7 days after second injection within the surveillance period.
2. VE(%) =100 × (1-RR) in SARS-CoV-2-naive (confirmed seronegative by anti-NP and no active COVID-19 infection by PCR test at baseline) adults who received both doses of study vaccine (NVX-CoV2373 or placebo) in the pre-crossover period. RR is ratio of incidence rates of active group relative to the placebo arm (NVX-CoV2373/placebo) with first occurrence of event with onset during a surveillance period from 7 days after second injection up to censor date. Participants were censored at the earliest of (i) cutoff date (August 9, 2021), (ii) date of major protocol deviation, (iii) date of death, (iv) date of unblinding (including for intended receipt of alternative COVID-19 vaccine), (v) early withdrawal, or (vi) first dose of crossover. PCR-positive participants who did not meet mild, moderate, or severe COVID-19 disease criteria were censored at date of the PCR-positive.

A secondary objective was to evaluate efficacy of a 2-dose regimen against PCR-confirmed symptomatic COVID-19 infection due to a SARS-CoV-2 variant not considered a VOC/VOI diagnosed ≥7 days after completion of Dose 2 of the initial vaccination. This objective could not be addressed because all sequenced cases were Delta variants.

Supportive analyses of PCR-confirmed COVID-19 cases any time after the first or second dose and any time after Dose 1 and before Dose 2 was performed using the PP-EFF-2 Set and the Full Analysis Set. In the PP-EFF-2 Set, which included those from the PP-EFF set with positive baseline serostatus, there were 17 cases of PCR-confirmed symptomatic mild, moderate, or severe COVID-19 with onset ≥7 days post the second dose. Five cases occurred in the NVX-CoV2373 arm and 12 cases occurred in the placebo arm; all cases were mild in severity. VE in the PP-EFF-2 set was 80.0% (95% CI: 43.1%, 92.9%).

In the FAS, there were 25 cases of PCR-confirmed COVID-19 with onset from first vaccination, with 10 (0.7%) in the NVX-CoV2373 group and 15 (2.0%) in the placebo group. All cases were mild. This analysis, which shows a lower VE of 67.04% (95% CI: 26.7%, 85.2%) compared to PP-EFF and PP-EFF-2, and cumulative event rates of infection are presented in Table 11.

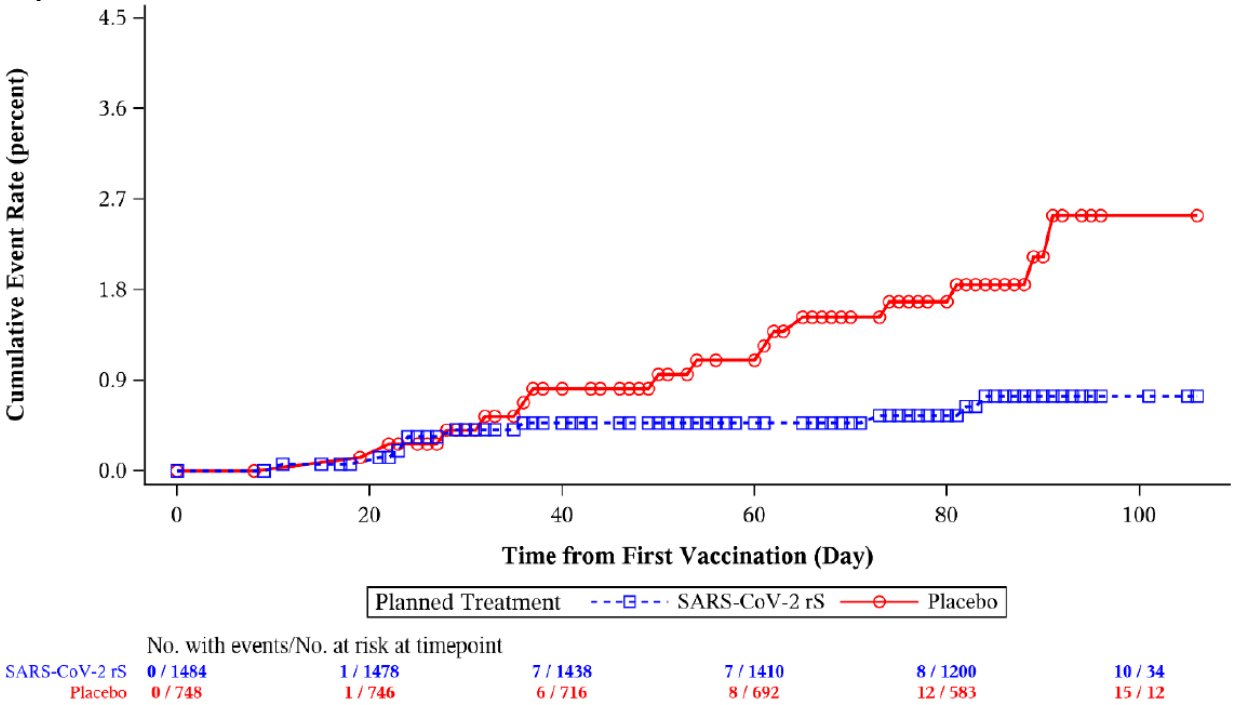
Table 11. Vaccine Efficacy and Cumulative Event rates of COVID-19 Cases With Onset From First Vaccination, Full Analysis Set

Parameter	NVX-CoV2373 N=1484	Placebo N=748
Participants with occurrence of event n (%)	10 (0.7)	15 (2.0)
Participants with no occurrence of event/censored n (%)	1474 (99.3)	733 (98.0)
Cumulative event rate % (95% CI)	--	--
7 Days after first vaccination	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
14 Days after first vaccination	0.1 (0.0, 0.4)	0.0 (0.0, 0.0)
21 Days after first vaccination	0.1 (0.0, 0.5)	0.1 (0.0, 0.7)
28 Days after first vaccination	0.3 (0.1, 0.8)	0.4 (0.1, 1.1)
3 Months after first vaccination	0.7 (0.4, 1.3)	2.1 (1.2, 3.5)
Vaccine Efficacy (%)	67.04	
95% CI	26.68, 85.18	

Source: IND 22430 Amendment 322, Tables 18 and 19.
Abbreviations: CI=confidence interval; COVID-19=coronavirus disease-2019; VE=vaccine efficacy; N=number of participants in Full Analysis Set for each study group; Event=first occurrence of PCR-confirmed mild, moderate, or severe COVID-19 with onset from first injection within the surveillance period, which is defined as first vaccination through the date of data cut or censoring event. Subjects were censored at the earliest of (i) cut-off date (August 9, 2021), (ii) date of death, (iii) date of unblinding (including for intended receipt of alternative COVID-19 vaccine), (iv) early withdrawal, or (v) first dose of crossover.

The cumulative incidence of COVID-19 in the FAS began to diverge between 20 to 40 days after Dose 1 (Figure 1). There were no cases of moderate to severe COVID-19 through the cleaned data cutoff date of August 9, 2021.

Figure 1. Cumulative Incidence Curve of PCR-Confirmed Mild, Moderate, or Severe COVID-19 With Onset From First Vaccination in Adolescent Participants Who Received at Least One Dose of Study Vaccine Regardless of Baseline Serostatus, Full Analysis Set, Study 301 Adolescent Expansion



Source: EUA 28237 Amendment 322, Figure 1.
Abbreviations: COVID-19=coronavirus disease 2019; PCR=polymerase chain reaction

Vaccine Efficacy in Protecting Against PCR-Confirmed COVID-19 in Demographic Subgroups

Vaccine efficacy was estimated for prespecified subgroups, which are presented in Table 12. With the exception of 12-14-year olds, female participants, and White and non-Hispanic participants, a reliable point estimate of VE could not be attained for the demographic subgroups due to lack of or insufficient cases of the primary endpoint.

Table 12. Analysis of Efficacy by Demographics and COVID-19 Risk Conditions, COVID-19 Starting 7 Days After Dose 2 in Baseline Seronegative/PCR-negative Participants 12-17 Years of Age, Per-Protocol Efficacy Set

Parameter	NVX-CoV2373 Cases[1] /N (%)	Placebo Cases[1] /N (%)	Vaccine Efficacy % (95% CI)
Final analysis of the primary endpoint	5/1205 (0.4)	11/594 (1.9)	78.29 (37.55, 92.45)[2]
Age (years)	--	--	--
12-14 years of age	3/822 (0.4)	7/407 (1.7)	79.25 (19.77, 94.63)[2]
15-17 years of age	2/383 (0.5)	4/187 (2.1)	76.81 (-26.23, 95.74)[2]
Sex	--	--	--
Male	2/622 (0.3)	3/328 (0.9)	66.12 (−103.22, 94.35)[2]
Female	3/583 (0.5)	8/266 (3.0)	83.32 (37.34, 95.56)[2]

Parameter	NVX-CoV2373 Cases[1] /N (%)	Placebo Cases[1] /N (%)	Vaccine Efficacy % (95% CI)
Race	--	--	--
White	5/922 (0.5)	10/447 (2.2)	76.58 (31.51, 91.99)[2]
Non-White	0/276 (0)	1/143 (0.7)	100.00 (-1896.35, 100.00)[3]
Mixed Origin	0/67 (0)	1/33 (3.0)	100.00 (-1871.36, 100.00)[3]
Ethnicity	--	--	--
Hispanic or Latino	0/185 (0)	1/100 (1.0)	100.00 (-1928.80, 100.00)[3]
Not Hispanic or Latino	5/1015 (0.5)	10/494 (2.0)	76.39 (31.02, 91.92)[2]

Source: IND 22430, Amendment 322, Table 15.
Abbreviations: CI=confidence interval; COVID-19=coronavirus disease-2019; PCR=polymerase chain reaction; RR=relative risk; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2
1. Case defined as first occurrence of PCR-confirmed mild, moderate or severe COVID-19 disease with onset from 7 days after second injection within the surveillance period.
2. VE (%)=100 × (1-RR) in SARS-CoV-2-naive (confirmed seronegative by anti-NP and no active COVID-19 infection by PCR test at baseline) adults who received both doses of study vaccine (NVX-CoV2373 or placebo) in the pre-crossover period. Participants were censored at the earliest of (i) cutoff date (August 9, 2021), (ii) date of major protocol deviation, (iii) date of death, (iv) date of unblinding (including for intended receipt of alternative COVID-19 vaccine), (v) early withdrawal, or (vi) first dose of crossover. PCR-positive participants who did not meet mild, moderate, or severe COVID-19 disease criteria were censored at date of the PCR-positive. VE is based on Log-linear model of occurrence using modified Poisson regression with logarithmic link function, treatment group and strata (age-group and pooled region) as fixed effects and robust error variance [Zou 2004] fitted separately to each subgroup.
3. In case when there are zero cases in either treatment group or the total number of cases in both treatment groups combined <5, VE and 95% CI is calculated using the Clopper-Pearson exact binomial method that conditions on the total number of cases and is adjusted for total surveillance time.

Secondary Immunogenicity Analyses

The secondary immunogenicity objective was to assess neutralizing antibody responses to SARS-CoV-2 regardless of baseline SARS-CoV-2 serostatus (PP-IMM-2 analysis set). As shown in Table 13, the fold-rise in GMT from baseline to Day 35 was more pronounced in seronegative adolescents (n=390; 372.5 [95% CI: 239.1, 421.5]) than in seropositive adolescents (n=74; 67.7 [95% CI: 48.8, 93.9]). Seroconversion rates, however, were similar at 98.7% and 98.6%, respectively.

Table 13. SARS-CoV-2 Neutralizing GMTs at Day 0 (Baseline) and Day 35 (14 Days After Second Vaccination) in Adolescent Participants by Baseline Serostatus, PP-IMM-2 Analysis Set

Parameter	NVX-CoV2373 N=464	NVX-CoV2373 N=390	NVX-CoV2373 N=74
Baseline serostatus	Negative or positive	Negative	Positive
Day 0 (baseline)[1]	--	--	--
n1	464	390	74
Median (1/dilution)	10.0	10.0	160.0
Min, max (1/dilution)	10, 2560	10, 1280	10, 2560
GMT	15.6	10.4	135.2
95% CI[2]	14.1, 17.3	10.0, 10.7	101.8, 179.5
Day 35	--	--	--
n1	464	390	74
Median (1/dilution)	5120.0	5120.0	10240.0
Min, max (1/dilution)	10, 81920	10, 81920	320, 81920
GMT	4429.3	3859.6	9151.3
95% CI[2]	3964.9, 4948.2	3422.8, 4352.1	7291.8, 11485.1
n2	464	390	74
GMFR referencing Day 0	**283.8**	**372.5**	**67.7**
95% CI[2]	249.4, 322.9	329.1, 421.5	48.8, 93.9
SCR ≥4-fold increase, n3/n2 (%)[3]	458/464 (**98.7**)	385/390 (**98.7**)	73/74 (**98.6**)
95% CI[4]	97.2, 99.5	97.0, 99.6	92.7, 100.0

Source: IND 22430 Amendment 322, Table 23.
Assay: microneutralization assay using SARS-CoV-2 Wild-Type Virus
Abbreviations: CI=confidence interval; GMFR=geometric mean fold rise; GMT=geometric mean titer; LLOQ=lower limit of quantification; max=maximum; min=minimum; MN=microneutralization; n1=number of participants in the PP-IMM-2 Analysis Set with non-missing data at visit; n2=number of participants in the PP-IMM-2 Analysis Set with non-missing data at both the baseline and Day 35 visit; n3=number of participants who reported ≥4-fold increase; PP-IMM-2=Per-Protocol Immunogenicity 2; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SCR=seroconversion rate.
1. Day 0 (baseline) was defined as the last non-missing assessment prior to study vaccine administration.
2. The 95% CI for GMT and GMFR were calculated based on the t-distr bution of the log-transformed values, then back transformed to the original scale for presentation.
3. The SCR percentage was defined as percentage of participants at each post vaccination visit with a ≥ 4-fold rise in antibody concentration.
4. The 95% CI for SCR percentage was calculated using the exact Clopper-Pearson method.
Note: Titer values less than LLOQ (20) were replaced by 0.5 × LLOQ. Percentages were calculated based on n2 as the denominator.

6.2.5 Safety

6.2.5.1 Safety Overview

Safety analyses presented in this review were based on data from the October 6, 2021 extraction date (see Table 15). As described in Section 6.2.1, participants could cross over to receive either placebo or NVX-CoV2373 in a blinded fashion. Therefore, data collected in the pre-crossover period provides placebo-controlled data, whereas data collected in the post-crossover period are only from participants who received NVX-CoV2373 at some point during the study. The duration of safety follow-up for the pre- and post-crossover periods is described in Table 14.

Also, the Sponsor provided additional supportive safety data (see Section 6.2.5.8) from a later follow-up timepoint (MAAEs, SAEs, and AESIs based on an extraction date of March 17, 2022); this data was provided in an unblinded pediatric safety report prepared for the DSMB.

Table 14. Duration of Safety Follow-Up, Safety Analysis Set

Parameter	Initial Randomization to NVX-CoV2373 N=1487	Initial Randomization to Placebo N=745	Initial Randomization Total N=2232	Blinded Crossover NVX-CoV2373 to Placebo N=665	Blinded Crossover Placebo to NVX-CoV2373 N=1353	Blinded Crossover Total N=2018
Initial vaccination series	--	--	--	--	--	--
Completed 2 doses	1468	730	2198	NA	NA	NA
Median follow-up post-Dose 2 (days)[1]	71	71	71	NA	NA	NA
Completed at least 1 month follow-up post-Dose 2	1457	718	2175	NA	NA	NA
Completed at least 2 months follow-up post-Dose 2	1266	614	1880	NA	NA	NA
Crossover vaccination series	--	--	--	--	--	--
Completed 4 doses	NA	NA	NA	638	1306	1944
Median follow-up post-Dose 4 (days)[1]	NA	NA	NA	30	30	30
Completed at least 1 month follow-up post-Dose 4	NA	NA	NA	275	541	816
Completed at least 2 months follow-up post-Dose 4	NA	NA	NA	0	0	0

Source: EUA 28237 Amendment 49, Table 4.
Abbreviations: NA=not applicable
1. Follow up days is the number of days between date of post-Dose 2 in the initial period and the earliest of (i) date of crossover, (ii)date of death, (iii) date of study termination, and (iv) October 6, 2021.

Table 15. Safety Overview, Safety Analysis Set

Participants Reporting at Least One	NVX-CoV2373 n/N (%)	Placebo n/N (%)
Solicited injection site reaction within 7 days	--	--
Dose 1 (Grade ≥1)	948/1448 (65.5)	207/726 (28.5)
Grade 3	22/1448 (1.5)	5/726 (0.7)
Grade 4	0	0
Dose 2 (Grade ≥1)	1050/1394 (75.3)	141/686 (20.6)
Grade 3	118/1394 (8.5)	4/686 (0.6)
Grade 4	0	0
Solicited systemic adverse reaction within 7 days	--	--
Dose 1 (Grade ≥1)	800/1448 (55.2)	296/726 (40.8)
Grade 3	52/1448 (3.6)	25/726 (3.4)
Grade 4	2/1448 (0.1)	0
Dose 2 (Grade ≥1)	1038/1394 (74.5)	198/686 (28.9)
Grade 3	304/1394 (21.8)	23/686 (3.4)
Grade 4	2/1394 (0.1)	0
Unsolicited adverse event[1]	--	--
Non-serious unsolicited AE	--	--
Pre-crossover period	230/1487 (15.5)	114/745 (15.3)
Post-crossover period	111/665 (16.7)	154/1353 (11.4)
Related non-serious unsolicited AE		
Pre-crossover period	43/1487 (2.9)	7/745 (0.9)
Post-crossover period	45/665(6.8)	11/1353 (0.8)
Grade 3 non-serious unsolicited AE	--	--
Pre-crossover period	2/1487 (0.1)	1/745 (0.1)
Post-crossover period	2/665 (0.3)	3/1353 (0.2)
Related Grade 3 non-serious unsolicited AE	--	--
Pre-crossover period	0	0
Post-crossover period	0	0
Medically attended adverse event	--	--
Pre-crossover period	96/1487 (6.5)	51/745 (6.8)
Post-crossover period	42/665 (6.3)	83/1353 (6.1)
Related MAAE	--	--
Pre-crossover period	5/1487 (0.3)	3/745 (0.4)
Post-crossover period	4/665 (0.6)	5/1353 (0.4)
SAE	--	--
Pre-crossover period	7/1487 (0.5)	2/745 (0.3)
Post-crossover period	3/665 (0.5)	2/1353 (0.1)
Related SAE	--	--
Pre-crossover period	0	0
Post-crossover period	1/665 (0.2)	0
AESI (PIMMCs)[2]	--	--
Pre-crossover period	0	0
Post-crossover period	0	0
AESI (PIMMCs)[3]	--	--
Pre-crossover period	1/1487 (<0.1)	0
Post-crossover period	0	1/1353 (<0.1)
AESI (PIMMCs)[4]	--	--
Pre-crossover period	1/1487 (<0.1)	0
Post-crossover period	0	1/1353 (<0.1)

Participants Reporting at Least One	NVX-CoV2373 n/N (%)	Placebo n/N (%)
AESI (related to COVID-19)	--	--
Pre-crossover period	0	0
Post-crossover period	0	0
Deaths	--	--
Pre-crossover period	0	0
Post-crossover period	0	0
AE leading to discontinuation of the vaccine	--	--
Pre-crossover period	1/1487 (<0.1)	1/745 (0.1)
Post-crossover period	0	0

Source: EUA 28237 Amendment 61, Response to IR #57, Table 6.
Abbreviations: AE=adverse event; AESI=adverse event of special interest; MAAE=medically attended adverse event; PIMMC=potential immune-mediated medical condition; SAE=serious adverse event
1. Reported within 28 days of any dose.
2. Based on investigator reporting.
3. Based on protocol-defined criteria.
4. Based on investigator reporting and protocol-defined criteria.

AEs Leading to Discontinuation

Two AEs leading to discontinuation of the vaccine occurred during the pre-crossover period, neither of which were considered related by the FDA:

- One NVX-CoV2373 recipient withdrew due to juvenile myoclonic epilepsy on Day 23 (see Section 6.2.5.6 for additional details).
- One placebo recipient withdrew due to rhinorrhea on Day 21.

No AEs leading to discontinuation occurred post-crossover.

AEs Leading to Withdrawal

No participant withdrew from the study due to AEs.

6.2.5.2 Solicited Adverse Reactions

Local Adverse Reactions

All solicited local ARs were reported by a higher proportion of participants in the NVX-CoV2373 arm than in the placebo arm, and the proportion of participants reporting solicited local reactions increased after the second dose of NVX-CoV2373 (Table 16). In both study groups, the most frequently reported local AR was injection site pain/tenderness. Grade 3 ARs were reported by a higher proportion of participants in the NVX-CoV2373 arm than in the placebo arm and increased in frequency following the second dose of NVX-CoV2373. No Grade 4 ARs occurred in either study group.

Table 16. Frequency of Solicited Local Adverse Reactions Within 7 Days After Each Dose, Safety Analysis Set

Event	NVX-CoV2373 Dose 1 N=1448 n (%)	Placebo Dose 1 N=726 n (%)	NVX-CoV2373 Dose 2 N=1394 n (%)	Placebo Dose 2 N=686 n (%)
Any solicited local injection site reaction	--	--	--	--
Any (Grade ≥1)	948 (65.5)	207 (28.5)	1050 (75.3)	141 (20.6)
Grade 3	22 (1.5)	5 (0.7)	118 (8.5)	4 (0.6)
Pain/tenderness	--	--	--	--
Any (Grade ≥1)	945 (65.3)	204 (28.1)	1045 (75.0)	141 (20.6)
Grade 3	22 (1.5)	4 (0.6)	108 (7.8)	4 (0.6)
Erythema	--	--	--	--
Any (Grade ≥1)	15 (1.0)	5 (0.7)	104 (7.5)	0
Grade 3	0	0	10 (0.7)	0
Swelling	--	--	--	--
Any (Grade ≥1)	20 (1.4)	3 (0.4)	111 (8.0)	1 (0.2)
Grade 3	0	1 (0.1)	8 (0.6)	0

Source: EUA 28237 Amendment 45, Table 1.
Abbreviations: n=number of participants experiencing the adverse event; N=number of participants in the Safety Analysis Set within each treatment arm who received the first dose (Dose 1) and second dose (Dose 2) and completed at least 1 day of the reactogenicity diary
Note: At each level of summarization, a participant is counted once if they indicated the event occurred and provided a severity during the reactogenicity period. The highest severity experienced during the reactogenicity period is summarized in this table.
Pain: Any: interferes with daily activities; Grade 3: Any use of narcotic pain reliever or prevents daily activity; Grade 4: ER visit or hospitalization.
Tenderness: Any: any discomfort to touch; Grade 3: Significant discomfort at rest; Grade 4: ER visit or hospitalization.
Erythema: Any: ≥2.5cm; Grade 3: >10 cm; Grade 4: Necrosis or exfoliative dermatitis.
Swelling/induration: Any: ≥2.5cm; Grade 3: >10 cm or prevents daily activity; Grade 4: Necrosis.
No NVX-CoV2373 or placebo recipient reported a Grade 4 reaction.

For any solicited local AR, the median time to onset was 1-3 days (range 1-7) for Doses 1 and 2 in both study arms. For each local AR, the median duration within the reactogenicity period of 7 days was between 1-3 days in the NVX-CoV2373 arm and 1-2 days in the placebo arm.

Solicited local ARs persisting beyond the 7-day reactogenicity period were reported by a higher proportion of participants in the NVX-CoV2373 arm (0.4% after Dose 1 and 0.1% after Dose 2) compared with the placebo arm (0% both doses). Of the local solicited ARs persisting beyond 7 days, pain/tenderness events were the most common.

In an analysis of local ARs by age group, all local ARs were reported in similar proportions for participants 12-15 years of age compared to participants 15-17 years of age. Overall rates of each local AR and Grade 3 ARs were similar in the 2 age cohorts. Table 17 provides rates of local ARs by treatment arm, dose, and age group. No NVX-CoV2373 or placebo recipient reported a Grade 4 local adverse reaction.

Table 17. Frequency of Solicited Local Reactions Within 7 Days After Each Dose, Safety Analysis Set

Event	NVX-CoV2373 Dose 1 N=971 (12 to 14) N=477 (15 to 17) n (%)	Placebo Dose 1 N=487 (12 to 14) N=239 (15 to 17) n (%)	NVX-CoV2373 Dose 2 N=936 (12 to 14) N=458 (15 to 17) n (%)	Placebo Dose 2 N=461 (12 to 14) N=225 (15 to 17) n (%)
Any solicited local injection site reaction, participants 12-14 years	--	--	--	--
Any (Grade ≥1)	639 (65.8)	151 (31.0)	709 (75.8)	108 (23.4)
Grade 3	16 (1.7)	2 (0.4)	79 (8.4)	3 (0.7)
Any solicited local injection site reaction, participants 15-17 years	--	--	--	--
Any (Grade ≥1)	309 (64.8)	56 (23.4)	341 (74.5)	33 (14.7)
Grade 3	6 (1.3)	3 (1.3)	39 (8.5)	1 (0.4)
Pain/tenderness, participants 12-14 years	--	--	--	--
Any (Grade ≥1)	637 (65.6)	150 (30.8)	705 (75.3)	108 (23.4)
Grade 3	16 (1.7)	2 (0.4)	73 (7.8)	3 (0.7)
Pain/tenderness, participants 15-17 years	--	--	--	--
Any (Grade ≥1)	308 (64.6)	54 (22.6)	340 (74.2)	33 (14.7)
Grade 3	6 (1.3)	2 (0.8)	35 (7.6)	1 (0.4)
Erythema, participants 12-14 years	--	--	--	--
Any (Grade ≥1)	11 (1.1)	3 (0.6)	71 (7.59)	0
Grade 3	0	0	6 (0.64)	0
Erythema, participants 15-17 years	--	--	--	--
Any (Grade ≥1)	4 (0.8)	2 (0.8)	33 (7.2)	0
Grade 3	0	0	4 (0.9)	0
Swelling, participants 12-14 years	--	--	--	--
Any (Grade ≥1)	11 (1.1)	2 (0.4)	78 (8.3)	1 (0.2)
Grade 3	0	0	4 (0.4)	0
Swelling, participants 15-17 years	--	--	--	--
Any (Grade ≥1)	9 (1.9)	1 (0.4)	33 (7.2)	0
Grade 3	0	1 (0.4)	4 (0.9)	0

Source: EUA 28237 Amendment 45, Tables 2 and 3.
Abbreviations: n=number of participants experiencing the adverse event; N=number of participants in the Safety Analysis Set within each treatment arm who received the first dose (Dose 1) and second dose (Dose 2) and completed at least 1 day of the reactogenicity diary
Note: At each level of summarization, a participant is counted once if they indicated the event occurred and provided a severity during the reactogenicity period. The highest severity experienced during the reactogenicity period is summarized in this table.
Pain: Any: interferes with daily activities; Grade 3: Any use of narcotic pain reliever or prevents daily activity; Grade 4: ER visit or hospitalization.

Tenderness: Any: any discomfort to touch; Grade 3: Significant discomfort at rest; Grade 4: ER visit or hospitalization.
Erythema: Any: ≥2.5cm; Grade 3: >10 cm; Grade 4: Necrosis or exfoliative dermatitis.
Swelling/induration: Any: ≥2.5cm; Grade 3: >10 cm or prevents daily activity; Grade 4: Necrosis.
No NVX-CoV2373 or placebo recipient reported a Grade 4 reaction.

Solicited Systemic Adverse Reactions

Solicited systemic ARs were reported by a higher proportion of participants in the NVX-CoV2373 arm compared to the placebo arm, overall and for each solicited AR. The proportion of participants with systemic solicited ARs after Dose 2 increased in the NVX-CoV2373 arm but remained comparable to after Dose 1 in the placebo arm. Grade 3 ARs were reported by a higher proportion of participants in the NVX-CoV2373 arm than in the placebo arm and increased in frequency following the second dose of NVX-CoV2373 (Table 18). Following Dose 2, 21.8% of participants reported any Grade 3 solicited systemic reaction; the most frequently reported Grade 3 systemic reactions were fatigue/malaise and myalgia. Two Grade 4 ARs of fever and one Grade 4 AR of headache occurred in the NVX-CoV2373 arm; no grade 4 ARs occurred in the placebo arm.

In both treatment groups and for both Dose 1 and 2, headache, fatigue/malaise, and muscle pain (myalgia) were the most commonly reported solicited systemic ARs.

Table 18. Frequency of Solicited Systemic Adverse Reactions Within 7 Days After Each Dose, Safety Analysis Set, Study 301 Adolescent Expansion

Event	NVX-CoV2373 Dose 1 N=1448 n (%)	Placebo Dose 1 N=726 n (%)	NVX-CoV2373 Dose 2 N=1394 n (%)	Placebo Dose 2 N=686 n (%)
Any solicited systemic reaction	--	--	--	--
Any (Grade ≥1)	800 (55.3)	296 (40.8)	1038 (74.5)	198 (28.9)
Grade 3	52 (3.6)	25 (3.4)	304 (21.8)	23 (3.4)
Grade 4	2 (0.1)	0	2 (0.1)	0
Fever	--	--	--	--
Any (Grade ≥1)	11 (0.8)	5 (0.7)	235 (16.9)	1 (0.2)
Grade 3	1 (0.1)	0	31 (2.2)	0
Grade 4	2 (0.1)	0	0	0
Headache	--	--	--	--
Any (Grade ≥1)	440 (30.4)	181 (24.9)	793 (56.9)	119 (17.4)
Grade 3	13 (0.9)	12 (1.7)	87 (6.2)	14 (2.0)
Grade 4	0	0	1 (0.1)	0
Fatigue/malaise	--	--	--	--
Any (Grade ≥1)	418 (28.9)	142 (19.6)	807 (57.9)	113 (16.5)
Grade 3	33 (2.3)	13 (1.8)	223 (16.0)	13 (1.9)
Grade 4	0	0	0	0
Muscle pain (myalgia)	--	--	--	--
Any (Grade ≥1)	492 (34.0)	114 (15.7)	683 (49.0)	82 (12.0)
Grade 3	17 (1.2)	4 (0.6)	104 (7.5)	6 (0.9)
Grade 4	0	0	0	0
Joint pain (arthralgia)	--	--	--	--
Any (Grade ≥1)	102 (7.0)	35 (4.8)	226 (16.2)	21 (3.1)
Grade 3	6 (0.4)	1 (0.1)	40 (2.9)	2 (0.3)
Grade 4	0	0	0	0

Event	NVX-CoV2373 Dose 1 N=1448 n (%)	Placebo Dose 1 N=726 n (%)	NVX-CoV2373 Dose 2 N=1394 n (%)	Placebo Dose 2 N=686 n (%)
Nausea/vomiting	--	--	--	--
Any (Grade ≥1)	113 (7.8)	56 (7.7)	277 (19.9)	33 (4.8)
Grade 3	2 (0.1)	3 (0.4)	14 (1.0)	3 (0.4)
Grade 4	0	0	1 (0.1)	0

Source: EUA 28237 Amendment 45, Table 4.
Abbreviations: ER=emergency room; IV=intravenous; n=unique number of participants experiencing the adverse event; N=number of participants in the Safety Analysis Set within each treatment arm who received the first dose (Dose 1) and second dose (Dose 2) and completed at least 1 day of the reactogenicity diary.
Note: At each level of summarization, a participant is counted once if they indicated the event occurred and provided a severity during the reactogenicity period. The highest severity experienced during the reactogenicity period is summarized in this table.
Fever: Any: ≥38.0; Grade 3: 39.0 to 40°C; Grade 4: >40°C.
Headache: Any: any interference with activity; Grade 3: Significant; any use of narcotic pain reliever or prevents daily activity; Grade 4: ER visit or hospitalization.
Fatigue/malaise, Myalgia/arthralgia: Any: any interference with activity; Grade 3: Significant; prevents daily activity; Grade 4: ER visit or hospitalization.
Nausea/vomiting: Any: any interference with activity or ≥1 episode/24 hours; Grade 3: Prevents daily activity, requires outpatient intravenous (IV) hydration; Grade 4: ER visit or hospitalization for hypotensive shock.

For any solicited systemic AR, the median time to onset was 2 days (range 1-7) for Doses 1 and 2 in both treatment arms. The median time to onset for each event was between 1 and 3 days, with the longest latency observed for joint pain and nausea following Dose 1 (3 days) in both treatment arms. For each systemic AR, the median duration within the reactogenicity period of 7 days was 1-2 days in both treatment arms.

Any solicited systemic AR persisting beyond the 7-day reactogenicity period was reported by a comparable proportion of participants in the NVX-CoV2373 arm (1% after Dose 1 and 0.6% after Dose 2) and the placebo arm (1% after Dose 1 and 0.7% after Dose 2). Of the solicited systemic ARs persisting beyond 7 days, headache was the most common event in both treatment arms.

In an analysis of systemic ARs by age group, all systemic ARs were reported in similar proportions for participants 12-15 years of age compared to participants 15 to 17 years of age. Overall rates of each systemic AR and Grade 3 or 4 ARs were similar in the 2 age cohorts. Table 19 provides rates of local ARs by treatment arm, dose, and age group.

Table 19. Frequency of Solicited Systemic Reactions Within 7 Days After Each Dose, Ad Hoc Dataset, Study 301 Adolescent Expansion

Event	NVX-CoV2373 Dose 1 N=971 (12 to 14) N=477 (15 to 17) n (%)	Placebo Dose 1 N=487 (12 to 14) N=239 (15 to 17) n (%)	NVX-CoV2373 Dose 2 N=936 (12 to 14) N=458 (15 to 17) n (%)	Placebo Dose 2 N=461 (12 to 14) N=225 (15 to 17) n (%)
Any solicited systemic reaction, participants 12-14 years	--	--	--	--
Any (Grade ≥1)	533 (54.9)	202 (41.5)	704 (75.2)	135 (29.3)
Grade 3	37 (3.8)	19 (3.9)	210 (22.4)	15 (3.3)
Grade 4	1 (0.1)	0	1 (0.1)	0
Any solicited systemic reaction, participants 15-17 years	--	--	--	--
Any (Grade ≥1)	267 (56.0)	94 (39.3)	334 (72.9)	63 (28.0)
Grade 3	15 (3.1)	6 (2.5)	94 (20.5)	8 (3.6)
Grade 4	1 (0.2)	0	1 (0.2)	0
Fever, participants 12-14 years	--	--	--	--
Any (Grade ≥1)	9 (0.9)	4 (0.8)	169 (18.1)	1 (0.2)
Grade 3	1 (0.1)	0	24 (2.6)	0
Grade 4	1 (0.1)	0	0	0
Fever, participants 15-17 years	--	--	--	--
Any (Grade ≥1)	2 (0.4)	1 (0.4)	66 (14.4)	0
Grade 3	0	0	7 (1.5)	0
Grade 4	1 (0.2)	0	0	0
Headache, participants 12-14 years	--	--	--	--
Any (Grade ≥1)	298 (30.7)	131 (26.9)	553 (59.1)	76 (16.5)
Grade 3	11 (1.1)	9 (1.9)	62 (6.6)	9 (2.0)
Grade 4	0	0	1 (0.1)	0
Headache, participants 15-17 years	--	--	--	--
Any (Grade ≥1)	142 (29.8)	50 (20.9)	240 (52.4)	43 (19.1)
Grade 3	2 (0.4)	3 (1.3)	25 (5.5)	5 (2.2)
Grade 4	0	0	0	0
Fatigue/malaise, participants 12-14 years	--	--	--	--
Any (Grade ≥1)	269 (27.7)	103 (21.2)	558 (59.6)	79 (17.1)
Grade 3	21 (2.2)	12 (2.5)	153 (16.4)	7 (1.5)
Grade 4	0	0	0	0

Event	NVX-CoV2373 Dose 1 N=971 (12 to 14) N=477 (15 to 17) n (%)	Placebo Dose 1 N=487 (12 to 14) N=239 (15 to 17) n (%)	NVX-CoV2373 Dose 2 N=936 (12 to 14) N=458 (15 to 17) n (%)	Placebo Dose 2 N=461 (12 to 14) N=225 (15 to 17) n (%)
Fatigue/malaise, participants 15-17 years	--	--	--	--
Any (Grade ≥1)	149 (31.2)	39 (16.3)	249 (54.4)	34 (15.1)
Grade 3	12 (2.5)	1 (0.4)	70 (15.3)	6 (2.7)
Grade 4	0	0	0	0
Muscle pain (myalgia), participants 12-14 years	--	--	--	--
Any (Grade ≥1)	334 (34.4)	82 (16.8)	472 (50.4)	56 (12.2)
Grade 3	15 (1.5)	2 (0.4)	66 (7.1)	5 (1.1)
Grade 4	0	0	0	0
Muscle pain (myalgia), participants 15-17 years	--	--	--	--
Any (Grade ≥1)	158 (33.1)	32 (13.4)	211 (46.1)	26 (11.6)
Grade 3	2 (0.4)	2 (0.8)	38 (8.3)	1 (0.4)
Grade 4	0	0	0	0
Joint pain (arthralgia), participants 12-14 years	--	--	--	--
Any (Grade ≥1)	71 (7.3)	21 (4.3)	148 (15.8)	14 (3.0)
Grade 3	5 (0.5)	1 (0.2)	19 (2.0)	2 (0.4)
Grade 4	0	0	0	0
Joint pain (arthralgia), participants 15-17 years	--	--	--	--
Any (Grade ≥1)	31 (6.5)	14 (5.9)	78 (17.0)	7 (3.1)
Grade 3	1 (0.2)	0	21 (4.6)	0
Grade 4	0	0	0	0
Nausea/vomiting, participants 12-14 years	--	--	--	--
Any (Grade ≥1)	78 (8.0)	39 (8.0)	194 (20.7)	23 (5.0)
Grade 3	2 (0.2)	3 (0.6)	11 (1.2)	2 (0.4)
Grade 4	0	0	0	0

Event	NVX-CoV2373 Dose 1 N=971 (12 to 14) N=477 (15 to 17) n (%)	Placebo Dose 1 N=487 (12 to 14) N=239 (15 to 17) n (%)	NVX-CoV2373 Dose 2 N=936 (12 to 14) N=458 (15 to 17) n (%)	Placebo Dose 2 N=461 (12 to 14) N=225 (15 to 17) n (%)
Nausea/vomiting, participants 15-17 years	--	--	--	--
Any (Grade ≥1)	35 (7.3)	17 (7.1)	83 (18.1)	10 (4.4)
Grade 3	0	0	3 (0.7)	1 (0.4)
Grade 4	0	0	1 (0.2)	0

Source: EUA 2837 Amendment 45, Tables 5 and 6.
Abbreviations: ER=emergency room; IV=intravenous; n=unique number of participants experiencing the adverse event; N=number of participants in the Safety Analysis Set within each treatment arm who received the first dose (Dose 1) and second dose (Dose 2) and completed at least 1 day of the reactogenicity diary
Note: At each level of summarization, a participant is counted once if they indicated the event occurred and provided a severity during the reactogenicity period. The highest severity experienced during the reactogenicity period is summarized in this table.
Fever: Any: ≥38.0; Grade 3: 39.0 to 40°C; Grade 4: >40°C.
Headache: Any: any interference with activity; Grade 3: Significant; any use of narcotic pain reliever or prevents daily activity; Grade 4: ER visit or hospitalization.
Fatigue/malaise, Myalgia/arthralgia: Any: any interference with activity; Grade 3: Significant; prevents daily activity; Grade 4: ER visit or hospitalization.
Nausea/vomiting: Any: any interference with activity or ≥1 episode/24 hours; Grade 3: Prevents daily activity, requires outpatient intravenous (IV) hydration; Grade 4: ER visit or hospitalization for hypotensive shock.

Immediate Adverse Events

The Sponsor did not categorize AEs that were immediate adverse events. In general, other than reactogenicity events, no pattern of concern was identified.

6.2.5.3 Unsolicited Adverse Events

Unsolicited Adverse Events (Pre-Crossover)

In the pre-crossover period, the proportions of participants reporting any non-serious unsolicited AE were comparable between the NVX-CoV2373 (15.5%) and placebo (15.3%) arms. Table 20 summarizes unsolicited AEs occurring in ≥1% of participants in a given Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) or Preferred Term (PT).

Table 20. Frequency of Unsolicited Adverse Events Reported With Occurrence in ≥1% of Participants, Study 301 Adolescent Expansion

Primary System Organ Class/ Preferred Term[1]	NVX-CoV2373 Any n/N (%)	NVX-CoV2373 Severe n/N (%)	Placebo Any n/N (%)	Placebo Severe n/N (%)
Pre-crossover period	--	--	--	--
Infections and infestations	61/1487 (4.1)	1/1487 (<0.1)	41/745 (5.5)	0
Upper respiratory tract infection	10/1487 (0.7)	0	14/745 (1.9)	0
General disorders and administration site conditions	34/1487 (2.3)	0	7/745 (0.9)	1/745 (0.1)
Nervous system disorders	24/1487 (1.6)	0	14/745 (1.9)	0
Headache	12/1487 (0.8)	0	8/745 (1.1)	0
Respiratory, thoracic and mediastinal disorders	42/1487 (2.8)	0	25/745 (3.4)	0
Cough	18/1487 (1.2)	0	6/745 (0.8)	0
Nasal congestion	21/1487 (1.4)	0	10/745 (1.3)	0
Oropharyngeal pain	16/1487 (1.1)	0	13/745 (1.7)	0
Rhinorrhea	6/1487 (0.4)	0	8/745 (1.1)	0
Gastrointestinal disorders	27/1487 (1.8)	1/1487 (< 0.1)	18/745 (2.4)	0
Musculoskeletal and connective tissue disorders	18 /1487 (1.2)	0	2/745 (0.3)	0
Skin and subcutaneous tissue disorders	21/1487 (1.4)	0	6/745 (0.8)	0
Injury, poisoning, and procedural complications	38/1487 (2.6)	1/1487 (<0.1)	15/745 (2.0)	0
Psychiatric disorders	22/1487 (1.5)	2/1487 (0.1)	9/745 (1.2)	1/745 (0.1)
Post-Crossover Period	--	--	--	--
Infections and infestations	31/665 (4.7)	1/665 (0.2)	78/1353 (5.8)	0
Upper respiratory tract infection	9/665 (1.4)	1/665 (0.2)	18/1353 (1.3)	0
Viral infection	10/665 (1.5)	0	19/1353 (1.4)	0
General disorders and administration site conditions	40/665 (6.0)	0	15/1353 (1.1)	2/1353 (0.1)
Injection site pain	8/665 (1.2)	0	4/1353 (0.3)	0
Pain	8/665 (1.2)	0	1/1353 (0.1)	0
Pyrexia	12/665 (1.8)	0	4/1353 (0.3)	2/1353 (0.1)

Primary System Organ Class/ Preferred Term[1]	NVX-CoV2373 Any n/N (%)	NVX-CoV2373 Severe n/N (%)	Placebo Any n/N (%)	Placebo Severe n/N (%)
Nervous system disorders	23/665 (3.5)	1/665 (0.2)	18/1353 (1.3)	0
Headache	19/665 (2.9)	1/665 (0.2)	13/1353 (1.0)	0
Respiratory, thoracic and mediastinal disorders	21/665 (3.2)	1/665 (0.2)	28/1353 (2.1)	0
Cough	8/665 (1.2)	0	8/1353 (0.6)	0
Nasal congestion	9/665 (1.4)	0	10/1353 (0.7)	0
Oropharyngeal pain	7/665 (1.1)	0	14/1353 (1.0)	0
Gastrointestinal disorders	12/665 (1.8)	0	16/1353 (1.2)	0
Injury, poisoning and procedural complications	8/665 (1.2)	0	20/1353 (1.5)	1/1353 (0.1)

Source: EUA 28237 Amendment 67, Table 8.
Abbreviations: AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; n=number of events reported; N=number of participants included in the considered cohort in each group
1. Adverse Events coded using MedDRA version 24.0.
Note: AEs were classified as treatment-emergent adverse events (TEAEs) or post-treatment and defined as any AE that was newly developed at or after the first dosing date of study vaccine. Unsolicited AEs, both pre- and post-crossover were collected from Dose 1 through the 28 days post-Dose 2; participants who only received the first dose in the pre- and post-crossover periods were monitored for non-serious unsolicited adverse events through 49 days after administration of vaccine or placebo.

Non-serious Grade 3 unsolicited events were reported by 0.1% of participants in the NVX-CoV2373 (n=2; pyrexia and appendicolith) and placebo (n=1; gastroenteritis) arms. None were considered related by the Investigator.

Non-serious unsolicited AEs considered related by the investigator were reported by 2.9% of participants in the NVX-CoV2373 arm and 0.8% of participants in the placebo arm. The most frequently reported related AEs in the NVX-CoV2373 arm included lymphadenopathy-related events, chills, diarrhea, and decreased appetite. Additional related AEs were consistent with local and systemic reactogenicity and included fatigue, arthralgia, injection site pruritis, and myalgia.

The most frequently reported (>1.0%) unsolicited AEs were consistent with common conditions in adolescents, including nasal congestion, cough, and oropharyngeal pain in the NVX-CoV2373 arm and upper respiratory tract infection, oropharyngeal pain, nasal congestion, headache, and rhinorrhea in the placebo arm.

Lymphadenopathy-related events (lymphadenopathy, axillary pain, and lymph node pain) were reported by 0.9% of participants in the NVX-CoV2373 arm and 0% of participants in the placebo arm and are considered plausibly related to vaccination. A plausible biological mechanism and imbalances in the following additional non-serious unsolicited events are suggestive of a causal relationship to NVX-CoV2373: fatigue (0.5% vaccine recipients vs. 0.0% placebo recipients), decreased appetite (0.3% vaccine recipients vs. 0.0% placebo recipients), arthralgia (0.2% vaccine recipients vs. 0.0% placebo recipients), injection site pruritus (0.2% vaccine recipients vs. 0.0% placebo recipients), and myalgia (0.1% vaccine recipients vs. 0.0% placebo recipients).

Unsolicited Adverse Events (Post-Crossover)

In the post-crossover period, the proportion of participants reporting any non-serious unsolicited AEs was greater in the arm that crossed over to receive NVX-CoV2373 (16.7%) compared to the arm that crossed over to receive placebo (11.4%).

Non-serious Grade 3 unsolicited events were reported by 0.3% of participants who crossed over to receive NVX-CoV2373 (n=2; upper respiratory tract infection and headache) and 0.2% of participants who crossed over to receive placebo (n=3; pyrexia, pyrexia, and muscle strain). None were considered related by the study investigator.

Unsolicited AEs considered related by the investigator were reported by 6.8% of participants who crossed over to receive NVX-CoV2373 and 0.8% of participants who crossed over to receive placebo. The most frequently reported (>1.0%) related AEs after NVX-CoV2373 were consistent with local and systemic reactogenicity, including pyrexia, pain, injection site pain, and headache. The most frequently reported (>1.0%) unsolicited AEs were consistent with common conditions in adolescents, including headache, pyrexia, viral infection, upper respiratory infection, nasal congestion, injection site pain, pain, cough, and oropharyngeal pain in participants who crossed over to receive NVX-CoV2373 and viral infection, upper respiratory infection, and headache in participants who crossed over to receive placebo.

Similar to the pre-crossover period, numerical imbalances were observed between the treatment arms, with events consistent with local and systemic reactogenicity (including injection site reactions, malaise, pain, chills, pyrexia, hot flush, vomiting, headache, and nausea) reported more frequently following crossover doses of NVX-CoV237 compared to placebo.

6.2.5.4 Unsolicited Adverse Events of Clinical Interest

Adverse Events of Special Interest

AESIs for Study 301 included PIMMCs and AEs representing complications specific to COVID-19. The AEs representing complications specific to COVID-19 were reviewed, and no concerns for vaccine enhanced disease were identified. PIMMCs are defined in Appendix A and are intended to capture potential autoimmune-mediated conditions that could be associated with adjuvanted vaccines. Three approaches were used to assess AESIs of PIMMCs in the study: 1) investigator reporting; 2) protocol-defined criteria; and 3) investigator reporting and protocol-defined criteria combined. The analyses that follow discuss only PIMMCs identified using protocol-defined criteria.

In the pre-crossover period, one SAE of seizure was reported in the NVX-CoV2373 arm that met protocol-defined criteria for a PIMMC. This event had a clear alternative etiology of preceding fluoxetine overdose. In the post-crossover period, there was one non-serious PIMMC of psoriasis (verbatim term infected scalp psoriasis on Day 8 post-Dose 3 of placebo (111 days following Dose 2 of NVX-CoV2373). No additional concern is raised in reviewing the identified PIMMCs.

Selected Safety Analyses

The following section includes search results from selected broad and narrow Standardized MedDRA Queries (SMQs) using FDA-developed software to evaluate unsolicited adverse events of clinical interest by searching PTs that could together represent various medical concepts. Based on safety information reviewed in the EUA request for adults ≥18 years, myocarditis/pericarditis, cardiac events, cardiac failure, hypersensitivity, hypertension, biliary events, uveitis, thrombotic and embolic events, and neurovascular events were further evaluated in adolescents. An imbalance in events of depression was identified and is described below.

Myocarditis/Pericarditis

A 16-year-old male experienced myocarditis two days after Dose 4 in the post-crossover period (following the second dose of NVX-CoV2373). The participant was hospitalized for four days and treated with intravenous immunoglobulin and had a peak troponin level of ~32,000 ng/L. The participant had a preceding nonspecific viral illness and concomitant methylphenidate use. This event was reported as resolved. Based on the timing of onset following vaccination and multiple similar cases of temporally related myocarditis and pericarditis, FDA considers this event related to NVX-CoV2373. Information on this and other events of myocarditis and pericarditis is included in the Fact Sheets for Novavax COVID-19 Vaccine, Adjuvanted.

Depression

Using the SMQ Depression (Broad), an imbalance in events of depression was identified in the pre-crossover period, with events of mild to moderate depression or depressed mood reported by 0.4% (n=6) of participants in the NVX-CoV2373 arm compared to no events in the placebo arm. The time to onset of the events ranged from 13 to 39 days. None of the events were serious. Among the 6 participants, 3 had a medical history of depression. One SAE of suicide and 2 events of intentional overdose/self-injury (1 serious and 1 nonserious) occurred in the NVX-CoV2373 arm, all of which occurred in participants with a medical history of anxiety or depression and with time to onset greater than 15 days after receipt of NVX-CoV2373. There were no suicide attempts or intentional overdose/self-injury events in the placebo arm.

In the post-crossover period, the SMQ Depression (Broad) identified 1 event of depression 8 days following crossover to NVX-CoV2373 and 2 events of depression/major depression in 2 participants 1 and 15 days, respectively, following crossover to placebo, 1 of whom had a history of major depression and also reported an event of intentional self-harm.

Further evaluation of additional SAEs from supportive safety data through March 17, 2022, showed more suicide attempts and SAEs of depression in participants who crossed over to receive placebo (see Section 6.2.5.8). One participant who crossed over to receive NVX-CoV2373 reported an SAE of suicide attempt. Four participants who crossed over to receive placebo reported depression-related SAEs, including depression and major depression (n=1 each); suicidal ideation (n=3); and suicide attempt and intentional self-injury (n=1 each). The time to onset of these events ranged from 42 to 241 days after the most recent NVX-CoV2373 dose.

The imbalance in AEs of depression in the pre-crossover period and the frequency of events of suicidality and depression in long-term follow-up post-crossover are notable. However, despite the presence of a clear imbalance in the pre-crossover period, a similar imbalance was not observed in the post-crossover period. Second, there is no clear or known biologically plausible mechanism for NVX-Cov2373 to cause depression or suicidality. Among the events, there is variability in the time to onset of events relative to receipt of NVX-CoV2373, without any clearly recognizable temporal pattern. Third, recent data from the CDC (https://www.cdc.gov/mmwr/volumes/71/su/su7103a3.htm) suggest that the COVID-19 pandemic has negatively affected the mental health of many children and adolescents and the number of events of depression and suicidality observed during the course of the study may reflect these findings. Therefore, the currently available information on events of depression and suicidality do not suggest a causal relationship with the vaccine.

All Cardiac Events

The SMQ Cardiac arrythmias (narrow and broad) was used to search for events reported within 7 days of vaccination in the pre-crossover period and identified events reported by 0.4% (n=6) of participants in the NVX-CoV2373 arm vs. 0 participants in the placebo arm. Reported events included syncope (n=3), heart rate increased (n=1), palpitations (n=1), and tachycardia (n=1). All of these events were mild and resolved without treatment. In the post-crossover period, use of the Cardiac arrhythmia SMQ identified more events within 7 days of vaccination in participants who received crossover placebo doses (0.2%; n=3) compared to those who received post-crossover NVX-CoV2373 doses (0 participants). The three events following placebo included sinus arrhythmia, supraventricular extrasystoles, and syncope. The risk of syncope is currently described in the Warnings section of the Novavax COVID-19 vaccine, Adjuvanted fact sheets. There is no clear pattern of events to suggest an association of NVX-CoV2373 with a specific arrhythmia within 7 days of vaccination.

Using the SMQ Cardiac failure (narrow and broad) to search for events in the pre- and post-crossover periods, no events were identified in the NVX-CoV2373 arm and 1 event of peripheral swelling (localized to the left thigh) was identified in the placebo arm during the pre-crossover period.

Hypersensitivity Reactions

Using the SMQs Angioedema and Hypersensitivity (narrow), a total of 18 events in 12 participants were identified within 7 days of any dose (including all 1,487 NVX-CoV2373 recipients and 745 placebo recipients in both the pre- and post-crossover periods). The most common preferred term was rash. There were 9 events of urticaria in 5 participants, including 4 participants (0.27%) in the NVX-CoV2373 arm and 1 (0.13%) in the placebo arm.

Hypertension, Biliary Events, Thrombotic, Neurovascular Events

There were no other notable events, patterns, or numerical imbalances between treatment groups for hypertensive, biliary, thrombotic, and neurovascular events that would suggest a causal relationship to NVX-CoV2373.

Guillain-Barre Syndrome/Neuropathy

Using the GBS (Broad) and Peripheral neuropathy (Broad) SMQ, no events were identified in either treatment arm that were consistent with Guillain-Barre syndrome (GBS) in either the pre- or post-crossover period.

Eye disorders

Using the SMQ Eye disorders (Broad), an imbalance in events was identified in the pre-crossover period, with eye disorders reported by 0.5% of participants in the NVX-CoV2373 arm (n=7) compared to 0.1% of participants in the placebo arm (n=1). Events in the NVX-CoV2373 arm included eye pruritis (n=2) and one event each of eye pain, eye irritation, myopia, chalazion, and eye irritation. The participant with eye pain had a history of migraines, Crohn's disease, and complex regional pain syndrome. The moderate eye pain started on Day 6, required ketorolac eye drops on Day 8, and per the investigator was not related to vaccine. The event recovered after 8 days. The event in the placebo arm was eye pruritis. None of the eye disorder events were considered related.

Post-crossover, ocular events included blepharospasm reported by 1 participant who crossed over to receive NVX-CoV2373 and blepharitis and blurred vision reported by 2 participants who crossed over to receive placebo. No events of uveitis/iridocyclitis were reported in the pre- or post-crossover periods.

There was no concerning pattern identified among the eye-related events.

6.2.5.5 Medically Attended Adverse Events

In the pre-crossover period, MAAEs were reported by 6.4% of participants in the NVX-CoV2373 arm and 6.8% of participants in the placebo arm. Related MAAEs were reported by 0.3% of participants in the NVX-CoV2373 arm and 0.4% of participants in the placebo arm. In the post-crossover period, MAAEs were reported by 6.3% of participants who crossed over to receive NVX-CoV2373 and 6.1% of participants who crossed over to receive placebo. Related MAAEs were reported by 0.6% of participants who crossed over to receive NVX-CoV2373 and 0.4% of participants who crossed over to receive placebo. In the pre-crossover period, 2 participants in the NVX-CoV2373 arm reported related MAAEs, both of which were of mild intensity, including pleurisy 2 days post-Dose 2 and events of mild chest discomfort, palpitations, and back pain managed with analgesics.

6.2.5.6 Serious Adverse Events (Pre-Crossover)

Deaths

There were no deaths reported among adolescent participants during the pre-crossover period.

Serious Adverse Events

In the pre-crossover period, SAEs were reported by 7 participants in the NVX-CoV2373 arm (0.5%) and 2 SAEs were reported by 2 participants in the placebo arm (0.2%). FDA agrees with the investigator's assessments that none of the events following NVX-CoV2373 were related to study vaccine.

Three psychiatric SAEs were reported in the NVX-CoV2373 arm. Please see Section 6.2.5.4 for additional discussion of events of depression.

- A 15-year old female participant with a history of anxiety and depression was hospitalized for intentional overdose of fluoxetine and seizure 36 days after Dose 2. In the preceding week, she had stress with her friendships and a disagreement with her mother.
- A 13-year old male participant with a history of autism, bipolar disease, anxiety, and attention deficit hyperactivity disorder was hospitalized due to an event of aggression 19 days after Dose 1. His aggressive behavior had increased over the prior month.
- A 13-year old female participant with a history of major depressive disorder was hospitalized for aspirin overdose 27 days after Dose 2.

Two SAEs in the NVX-CoV2373 arm had a clear alternative infectious etiology:

- A 17-year old female was hospitalized with norovirus gastroenteritis 11 days after Dose 1.
- A 13-year old male participant with a recent history of a trigger finger release was hospitalized with a methicillin-resistant *Staphylococcus aureus* infection of the left thumb 39 days after Dose 2.

The remaining 2 SAEs in the NVX-CoV2373 arm included:

- A 13-year-old male participant was hospitalized for splenic rupture 43 days after Dose 2 due to a fall from a bicycle. Trauma provides a clear alternative etiology for this event.
- A 14-year old male participant with a history of insomnia, anxiety and depression was hospitalized for juvenile monoclonal epilepsy on Day 22 following Dose 1 and treated with lamotrigine. Per the medical records, 1 year ago, the participant reported abnormal arm movements, abnormal speech, an occurrence of falling in the shower, eyes rolling back, moaning, and increased oral secretions. The episodes varied in duration and occurred more in the morning and when he was tired. The presence of neurologic symptoms preceding vaccination makes a causal relationship to vaccine unlikely.

The 2 SAEs in the placebo arm included events of mental status change 7 days after receiving Dose 2 and peritonsillar abscess 2 months after Dose 2.

6.2.5.7 Serious Adverse Events (Post-Crossover)

Deaths

There were no deaths among adolescent participants during the post-crossover period.

Serious Adverse Events

Although participants originally randomized to the NVX-CoV2373 arm crossed over to receive placebo and comparisons across crossover treatment arms may discern imbalances in adverse events manifesting shortly after vaccination, prior vaccination with NVX-CoV2373 must be considered in assessments of causality for events occurring in the post-crossover period.

In the post-crossover period 3 SAEs occurred in 3 participants who crossed over to receive NVX-CoV2373 (0.1%) and 3 SAEs occurred in 2 participants who crossed over to receive placebo (0.1%). With the exception of the event of myocarditis, FDA agrees with the investigator's assessments that none of the events were clearly related to study vaccine.

The following SAEs occurred in participants who crossed over to receive NVX-CoV2373:

- The serious event of myocarditis in a 16-year old male participant 2 days after Dose 4 is described in more detail in Section 6.2.5.4.
- A 13-year old female participant with a history of mild, intermittent asthma was seen in the Emergency Department 10 days after the first crossover dose of NVX-CoV2373 with an asthma exacerbation treated with albuterol. She was not admitted to the hospital and the seriousness criterion was a life-threatening event. The latency between vaccination and onset of the asthma exacerbation is not suggestive of a hypersensitivity reaction. Limited information on potential alternative etiologies, such as environmental or viral triggers, is not provided. Currently available information on this report is insufficient to determine a causal relationship with the vaccine.
- A 13-year old female participant with a history of mood disorder and attention deficit hyperactivity disorder was hospitalized 17 days after the first crossover dose of NVX-CoV2373 with an event of affective disorder (worsening of mood disorder). She was treated with bupropion. Her lisdexamfetamine was discontinued. Additional medical information was not provided. Please see Section 6.2.5.4 for additional discussion of events of depression.

The following SAEs occurred in participants who crossed over to receive placebo:

- A 14-year old female participant with a history of major depression and recurrent and mild intermittent anxiety was hospitalized due to worsening of major depression and intentional self-injury (cutting) 14 days after the first crossover dose of placebo and 77 days after the second dose of NVX-CoV2373. The events were attributed to recent family conflict. Please see Section 6.2.5.4 for additional discussion of events of depression.
- A 14-year old male participant with a history of anxiety and attention deficit hyperactivity disorder was hospitalized 6 days after the first crossover dose of placebo and 98 days after the second dose of NVX-CoV2373 with worsening anxiety (later revised to aggression). During hospitalization, treatment with aripiprazole was initiated. This event was attributed to a previously undiagnosed underlying psychiatric illness.

6.2.5.8 Serious Adverse Events Reported from Later Follow-Up

As described in Section 6.2.5.1, the Sponsor provided additional safety data available in the clinical database as of March 17, 2022, to allow FDA to conduct a cumulative safety evaluation through a more recent time point; however, this data is subject to change.

Review of the additional safety data identified an additional 9 participants with SAEs in the post-crossover period, including 2 participants who crossed over to receive NVX-CoV2373 and 7 participants who crossed over to receive placebo. The following SAEs were reported in participants who crossed over to receive NVX-CoV2373, both of which were considered not related to vaccine by the Investigator and FDA:

- A 15-year-old female participant with a history of suicidal ideation, self-injurious behavior, generalized anxiety disorder, autism spectrum disorder, and depression was hospitalized following an intentional drug overdose with aripiprazole 42 days after second crossover dose of NVX-CoV2373. The event was attributed to recent difficulties in school and other stressors. Please see Section 6.2.5.4 for additional discussion of events of depression.
- A 13-year-old female participant was hospitalized with malnutrition 68 days after the second dose of SARS-CoV-2 rS vaccine. She had a medical history of significant calorie restriction and excessive energy expenditure prior to participation in the study and was hospitalized in a specialized inpatient eating disorder unit for severe malnutrition secondary to anorexia nervosa. Due to the presence of symptoms of anorexia nervosa prior to study vaccination, the event of malnutrition is unlikely to be related to vaccination.

Of the 7 additional SAEs were reported in participants who crossed over to receive placebo, 4 included psychiatric events, all of which were considered unrelated by the Investigator. Please see Section 6.2.5.4 for additional discussion of events of depression.

- A 14 year-old female participant with a history of anxiety, attention deficit hyperactivity disorder, previous suicide attempt, and bipolar disorder was hospitalized with events of suicidal ideation and attempted suicide 98 days after the second crossover dose of placebo and 191 days after Dose 2 of NVX-CoV2373. She had not been on medications for over a year due to loss of health insurance. She was treated with anti-depressants and improved.
- A 14 year-old female participant with a history of depression and prior suicide attempts, attention deficit hyperactivity disorder, and anxiety was hospitalized due to worsening of depression and a suicide attempt 149 days after receiving second crossover dose of placebo and 241 days after Dose 2 of NVX-CoV2373.

- A 15 year-old female participant with a history of psoriasis was hospitalized for suicidal ideation 130 days after the second dose of crossover placebo and 233 days after Dose 2 of NVX-CoV2373.
- A 13 year-old female participant with a history of suicidal ideation was hospitalized for suicidal ideation 90 days after the first dose of crossover placebo and 168 days after Dose 2 of NVX-CoV2373.

The remaining 3 SAEs in participants who crossed over to receive placebo include the following:

- A 14 year-old female participant was hospitalized with an enlarged left ovary and complex hemorrhagic left ovarian cyst 24 days after the second crossover dose of placebo and 127 days after Dose 2 of NVX-CoV2373. There is no clear biologic mechanism to support a causal relationship to vaccine.
- A 12 year-old male participant was hospitalized for an allergic reaction (rash, fever, lip swelling, and difficulty breathing) 174 days after the second crossover dose of placebo and 270 days after Dose 2 of NVX-CoV2373. The prolonged latency between vaccination and onset of symptoms does not support a causal relationship to vaccination.
- A 13 year-old male participant with a history of asthma was hospitalized for an asthma attack 143 days after the second crossover dose of placebo and 230 days after Dose 2 of NVX-CoV2373. The asthma exacerbation was thought to have been triggered by exposure to construction dust and a tree mill near his home. The prolonged latency and plausible alternative etiology (environmental exposures in the context of existing asthma) do not support a causal relationship to vaccination.

6.2.5.9 Subgroup Analyses of Safety

Baseline serostatus

Lower rates of solicited local and systemic reactions were seen in participants who were baseline (pre-Dose 1) anti-NP/PCR SARS-CoV-2 positive relative to participants who were baseline anti-NP/PCR SARS-CoV-2 negative.

Race and ethnicity

Overall, the proportion of participants reporting different categories of AEs (solicited, unsolicited and SAEs) were comparable between subgroups by race and ethnicity. However, when comparing risk differences between the NVX-CoV2373 and placebo arms across the race groups, participants who are White and non-Hispanic had numerically higher rates of solicited AEs. Higher rates of unsolicited AEs were seen among White, mixed origin, and non-Hispanic or Latino participants. However, the comparator sample sizes are too small to make definitive conclusions.

Age

As compared with participants 15-17 years of age, participants 12-14 years of age had numerically higher local and systemic solicited events (see Section 6.2.5.2), with a slightly higher proportion of Grade 3 events in this younger age group. Unsolicited events were higher in participants 12 to 15 years of age; this was driven mainly by common AEs in the pediatric population (e.g., nasal congestion, headache).

Sex

Numerical differences were seen among female (n=731) participants for all solicited ARs (local and systemic) compared with males (n=756). Local solicited ARs after Dose 1 were reported in 74.1% and 69.9% in females vs. males, respectively. Local solicited ARs after Dose 2 were reported in 82.2% and 58.1% in females vs. males, respectively. The majority of these local reactions were pain and tenderness. Systemic solicited ARs with Dose 1 were reported in 64.2% and 46.6% in females vs. males, respectively. Systemic solicited ARs with Dose 2 were reported in 82.2% and 76.2% in females vs. males, respectively. Females had significantly more fatigue than males: Dose 1 (49.0% vs. 29.4%) and Dose 2 (50.7% vs. 19.2%). Grade 4 solicited reactions were infrequent in both females and males. Females had higher rates of unsolicited and severe unsolicited AEs, but no difference in treatment-related unsolicited AEs. The numerical differences in solicited reactions between subgroups of sex were noted in this sample of 730+ participants and may not be reflective in larger cohorts or be subject to bias.

No specific safety concerns were identified in subgroup analysis of solicited reactions by COVID-19 serostatus. No specific safety concerns were identified in subgroup analyses by age, sex, race, and ethnicity. Solicited, unsolicited, and serious adverse events in these subgroups were generally consistent with the overall study population.

6.2.5.10 Pregnancy

No pregnancies were reported through the October 6, 2021 extraction date. However, in the follow up period through March 17, 2022, a 16-year-old female participant became pregnant, with a positive pregnancy test in February 2022, and an estimated delivery date in October 2022. At the time of this memo, the outcome of the pregnancy is unknown.

6.2.6 Summary of Study 2019nCoV-301 Adolescent Expansion

Vaccine effectiveness in adolescents 12-17 years of age was inferred based on comparisons of neutralizing antibody response at Day 35 (pre-crossover period) in adolescent participants to that observed in participants 18-25 years of age from the same study. The point estimate of the ratio of GMTs in adolescents versus adults was 1.47 and the lower bound of the 95% CI was 1.26, both of which met the corresponding success criteria of ≥0.82 and >0.67. SCRs were similar in both age cohorts, and the lower bound of the 95% CI for difference in SCR among the adolescent cohort and the adult cohort was −2.75%, which met the corresponding success criterion of > −10%.

VE against central laboratory-confirmed mild, moderate, or severe COVID-19 was 78.3% (95% CI: 37.6, 92.5) for the prevention of PCR-confirmed symptomatic COVID-19 illness diagnosed ≥7 days after completion of the second NVX-CoV2373 vaccination in the pre-crossover period.

The available safety database (N=2,897; 2,152 vaccine, 745 placebo) meets the expectations in FDA's Guidance on Development and Licensure of Vaccines to Prevent COVID-19. Safety data from the October 6, 2021 extraction date serves as the primary basis of this EUA review and conclusions. FDA has independently verified the safety data with an extraction date of October 6, 2021, and analyzed additional data on deaths, PIMMCs, and SAEs through March 17, 2022. In the pre-crossover period, the median follow-up post-Dose 2 was 71 days; 85% of participants in the NVX-CoV2373 arm and 82% of participants in the placebo arm had safety follow-up for at least two months post-Dose 2. In the post-crossover period, the median follow-up post-Dose 4 was 30 days; 41% of participants in each treatment arm were followed for at least two months

post-Dose 4. The totality of the data package submitted to the EUA meets the Agency's expectations on the minimum duration of follow-up.

Local site reactions and systemic solicited events were more common after NVX-CoV2373 compared to placebo, with increased frequency and severity following the second dose. The most frequently reported local AR was injection site pain/tenderness. After NVX-CoV2373, any Grade 3 local AR was reported by 1.5% of participants post-Dose 1 and 8.5% of participants post-Dose 2, and no grade 4 local ARs were reported. The median time to onset for any local AR was 1-3 days following vaccination and the median duration was 1-2 days. After NVX-CoV2373, Grade 3 and 4 solicited systemic ARs were reported by 3.6% and 0.1% of participants, respectively, post-Dose 1 and by 21.8% and 0.1% of participants, respectively, post-Dose 2. In both treatment groups and for both Dose 1 and 2, headache, fatigue/malaise, and muscle pain (myalgia) were the most commonly reported solicited systemic ARs. For any solicited systemic AR, the median time to onset was 2-4 days and the median duration was 1-2 days for Doses 1 and 2 in both treatment arms.

One event of myocarditis was reported in temporal relationship to NVX-CoV2373, and FDA considers this event to be related to vaccination. Events of lymphadenopathy were infrequent but reported by a higher proportion of participants in the NVX-CoV2373 arm (0.9%). Imbalances in the following additional non-serious unsolicited events are suggestive of a causal relationship to NVX-CoV2373: fatigue (0.5% vaccine recipients vs. 0.0% placebo recipients), decreased appetite (0.3% vaccine recipients vs. 0.0% placebo recipients), arthralgia (0.2% vaccine recipients vs. 0.0% placebo recipients), injection site pruritus (0.2% vaccine recipients vs. 0.0% placebo recipients), and myalgia (0.1% vaccine recipients vs. 0.0% placebo recipients). Hypersensitivity reactions, namely urticaria, were reported in more participants following NVX-CoV2373 (0.3%) than following placebo (0.1%). Review of the data also identified a numerical imbalance in events of depression and suicidality, although the available data do not suggest a causal relationship with the vaccine.

7. Foreign Postmarketing Experience

Very limited postmarketing safety data are available regarding use of Novavax COVID-19 Vaccine in adolescents. According to the Sponsor's most recently reviewed Summary Safety Report for reporting period of July 1, 2022, to July 31, 2022, among countries/jurisdictions reporting vaccine administration data by age group, there were cumulative 258 vaccine administrations reported for the pediatric age group (<18 years). Of the cumulative 2,128 spontaneous Individual Case Safety Reports (ICSRs) received, only 17 ICSRs were for individuals under age 18 years. These 17 ICSRs identified 36 adverse events (AEs) including one serious and 10 non-serious medically confirmed AEs, and 25 non-serious, non-medically confirmed AEs. The Sponsor did not identify any trends in AEs to suggest a new safety signal in this population.

The FDA queried the World Health Organization's VigiBase on August 12, 2022 (UMC, 2021). VigiBase is a global database of reported potential side effects of medicinal products, developed and maintained by Uppsala Monitoring Centre (UMC), with around 150 actively contributing countries (UMC, 2022a). The information presented here does not represent the opinion of the UMC or the World Health Organization. Reports come from a variety of sources and the probability that the suspected adverse effect is drug-related is not the same in all cases. For additional details on the limitations and conditions of VigiBase, see the UMC Caveat Document (UMC, 2022b). This query revealed a total of 2,091 reports for Novavax COVID-19 Vaccine. Of

these reports, only 12 reports (0.6%) were for individuals aged 12-17 years. Five reports were in females and seven reports were in males. All reports were non-serious and were from Australia. There were no findings in the reported adverse events to suggest a new safety signal.

8. FDA Review of Other Information Submitted

8.1 Chemistry, Manufacturing, and Control (CMC) Information

The Novavax COVID-19 Vaccine, Adjuvanted (NVX-CoV2373 vaccine) contains a recombinant full-length SARS-CoV-2 spike glycoprotein (rS) that is expressed from a recombinant baculovirus vector in *Spodoptera frugiperda* insect cells, purified by (b) (4) chromatography and formulated in a buffer containing sodium phosphate, sodium chloride, and polysorbate 80. The drug product (DP) is a co-formulation of the rS antigen drug substance (DS) with Matrix-M, a saponin-based adjuvant derived from the bark of *Quillaja saponaria* Molina and formed into matrix particles with phosphatidylcholine and cholesterol.

Production of the (b) (4) for clinical development has evolved from a (b) (4) scale, produced at one Contract Manufacturing Organization (CMO) for Phase 1/Phase 2 trials, to a (b) (4) scale produced at a different CMO for Phase 3 study. The EUA request is also based on a (b) (4) process; however, the intended commercial product is being produced at a manufacturing facility that is different from the CMO that produced the clinical trial material (CTM) for Phase 3 study. A comprehensive analytical comparability assessment has been performed and the data support quality comparability of (b) (4) DS lots from the supply site for Phase 3 and the (b) (4) DS lots from the facility supporting the EUA.

Matrix-M is manufactured by mixing Matrix-A and Matrix-C, each of which is produced separately as a mixture of saponin extracts and lipid solutions. Comprehensive analytical comparability assessments have been performed and the data submitted support the comparability of Matrix-A and Matrix-C produced from three different manufacturing facilities.

The NVX-CoV2373 drug product (DP) is manufactured by mixing the rS antigen DS with Matrix-A and Matrix-C followed by sterile filtration and fill/finish. Like the DS production, the CTM DP lots were produced at a smaller scale at a CMO that was different from the facility supporting the EUA request. The commercial scale DP process for the EUA request was validated and a comprehensive analytical comparability assessment has been performed. The data support quality comparability of DP lots from the supply site for Phase 3 trial and the DP lots from the production site supporting the EUA. The Sponsor will submit the Certificates of Analysis of DP lots to be distributed under EUA for review at least 48 hours prior to lot distribution.

Stability studies have been designed to support use of the vaccine under the EUA. All available stability data generated with NVX-CoV2373 DS and DP lots support the emergency deployment of Novavax COVID-19 Vaccine, Adjuvanted. All stability studies of the DS and DP lots are ongoing and will continue to be monitored. Data will be submitted to the EUA as they become available.

The analytical methods for the assessment of critical quality attributes (identity, purity, quality, and potency) of the DS and DP for product release and stability evaluation have been qualified/validated for performance and met pre-specified acceptance criteria for accuracy, inter- and intra-assay precision, specificity, and sensitivity, and are suitable for the intended use.

8.2 Pharmacovigilance Activities

The Sponsor submitted an updated Pharmacovigilance Plan (Version 0.3, dated June 27, 2022) to monitor safety concerns that could be associated with the Novavax COVID-19 Vaccine. The Sponsor included anaphylaxis and myocarditis and/or pericarditis as important identified risks. Vaccine-associated enhanced disease including vaccine-associated enhanced respiratory disease is an important potential risk. Use in pregnancy and while breast feeding, use in immunocompromised patients, use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders), use in patients with autoimmune or inflammatory disorders, interaction with other vaccines, and long-term safety are areas the Sponsor identified as missing information.

The Sponsor will conduct both passive and active surveillance activities for continued vaccine safety monitoring. Passive surveillance activities will include submitting spontaneous reports of the following events to the Vaccine Adverse Event Reporting System (VAERS) within 15 days:

- Serious adverse events (irrespective of attribution to vaccination)
- Cases of Multisystem Inflammatory Syndrome in adults and children
- Cases of COVID-19 that result in hospitalization or death

The Sponsor will also conduct periodic aggregate review of safety data and submit periodic safety reports in accordance with a reporting interval and due date agreed upon with the Office of Biostatistics and Pharmacovigilance (OBPV). Each periodic safety report is required to contain descriptive information which includes:

- A narrative summary and analysis of adverse events submitted during the reporting interval, including interval and cumulative counts by age groups, special populations (e.g., pregnant women), and adverse events of special interest
- A narrative summary and analysis of vaccine administration errors, whether or not associated with an adverse event, that were identified since the last reporting interval
- Newly identified safety concerns in the interval
- Actions taken since the last report because of adverse experiences (e.g., changes made to Vaccination Provider fact sheets, changes made to studies or studies initiated)

The Sponsor studies will include completion of long-term follow-up from ongoing clinical trials as well as the following five planned surveillance studies.

- Pregnancy Exposure Registry: The Sponsor plans to use the COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER)—a multi-country, observational, prospective cohort study of women vaccinated during pregnancy with a COVID-19 vaccine—to evaluate obstetric, neonatal, and infant outcomes among women vaccinated during pregnancy with the Novavax COVID-19 Vaccine. The planned study duration is 48 months for enrollment and follow-up of participants.
- US Active Follow-Up for Safety: This is an active safety surveillance study to evaluate the risk of select AESIs in association with administration of the Novavax COVID-19 Vaccine in adults 18 years of age and older in the real-world setting in the US. The Sponsor plans to use a large US-based insurance claims database and/or electronic health records database. The study design includes two methods: 1) a self-controlled case series design and 2) a retrospective comparative matched cohort study design. The planned study duration is 30

months following receipt of regulatory authorization of the Novavax COVID-19 Vaccine in the US.

- UK Active Follow-Up for Safety: This is an active safety surveillance study to evaluate the risk of select AESIs in association with administration of the Novavax COVID-19 Vaccine in adults 18 years of age and older in the real-world setting in the United Kingdom (UK). The Sponsor plans to use the Clinical Practice Research Datalink and associated linked databases for this study. The study design includes two methods: 1) a self-controlled case series design and 2) a retrospective comparative matched cohort study design. The planned study duration is 30 months following receipt of regulatory authorization of the Novavax COVID-19 Vaccine in the UK.
- US Real World Effectiveness Study: This study is a real-world effectiveness study to assess the effectiveness of the Novavax COVID-19 Vaccine in preventing SARS-CoV-2 infection in adults 18 years of age and older in the US. The Sponsor plans to use a large US-based insurance claims database and/or electronic health records database. The study design is a retrospective comparative cohort study design. The planned study duration is 30 months following FDA concurrence on the final study protocol.
- European Real World Effectiveness Study: This is a real-world effectiveness study to assess the effectiveness of the Novavax COVID-19 Vaccine against hospitalization due to laboratory-confirmed SARS-CoV-2 in adults 18 years of age and older in multiple European countries. The Sponsor plans to use COVIDRIVE, a multi-stakeholder, public-private partnership program, as the data source. The study is a prospective, hospital-based case-control study using a test-negative design. The planned duration of the study is a minimum of one year with an expected study duration of two years.

With the exception of the pregnancy exposure registry, the Sponsor agreed to update the protocols for each post-authorization study to include adolescents aged 12 to <18 years old.

FDA will provide feedback on these studies after further review of protocols once submitted by the Sponsor.

Reporting to VAERS and Novavax

Providers administering the Novavax COVID-19 Vaccine must report to VAERS (as required by the National Childhood Vaccine Injury Act) and to the extent feasible, report to Novavax, the following information associated with the vaccine of which they become aware:

- Vaccine administration errors whether or not associated with an adverse event
- Serious adverse events (irrespective of attribution to vaccination)
- Cases of Multisystem Inflammatory Syndrome in adults and children
- Cases of COVID-19 that result in hospitalization or death

Additional VAERS Reporting

An additional source of VAERS reports will be through a program administered by the CDC known as v-safe. V-safe is a smartphone-based opt-in program that uses text messaging and web surveys to help COVID-19 vaccine recipients monitor for and report side effects. The system also will provide telephone follow-up to anyone who reports medically important adverse events. Responses indicating missed work, inability to do normal daily activities, or receipt of care from a doctor or other healthcare professional will trigger the VAERS Call Center to reach out to the participant and collect information for a VAERS report, if appropriate.

8.3 Clinical Assay Information

The measurement of SARS-CoV-2-neutralizing antibodies induced by the NVX-CoV2373 vaccine is performed by microneutralization (MN) assay. In this assay, serum samples obtained from clinical studies are tested for the ability to block the infection of Vero E6 cells by a clinical isolate of SARS-CoV-2 (hCoV-19/Australia/VIC01/2020) *in vitro*. The MN assay was validated for precision, sensitivity (lower limit of quantitation and upper limit of quantitation), specificity and selectivity, and dilutional linearity. In addition, matrix effect, robustness and sample stability were evaluated in the validation study. COVID-19 convalescent serum samples, pre-COVID-19 serum samples, and incurred serum samples from the Phase 1 clinical evaluation of NVX-CoV2373 were used in the validation study. Data from the validation study show that acceptance criteria were met for each assay validation parameter, and support the utility of the MN assay in measuring the level of SARS-CoV-2-neutralizing antibody induced in vaccine recipients.

Two clinical diagnostic assays (Roche Elecsys anti-SARS-CoV-2 assay and Abbott RealTime Quantitative SARS-CoV-2 Assay) were used to assess clinical endpoints. Both assays have received FDA authorization under EUA. Prior to vaccination with NVX-CoV2373 or placebo, the baseline serostatus of study enrollees in the clinical trial was determined using the Roche Elecsys Anti-SARS-CoV-2 assay. The Elecsys anti-SARS-CoV-2 assay is an antibody-based electrochemiluminescence immunoassay used for the qualitative detection of antibodies to the nucleocapsid protein of SARS-CoV-2 in clinical serum and plasma samples. The diagnosis of SARS-CoV-2 infection during clinical study was confirmed with the Abbott RealTime Quantitative SARS-CoV-2 Assay that targets the amplification of unique regions of the RNA-dependent RNA polymerase and the N genes. Both the Roche Elecsys and the Abbott RealTime Quantitative SARS-CoV-2 Assay were validated for performance at the University of Washington (Novavax's testing site) and are suitable for utility in SARS-CoV-2 diagnosis.

8.4 BIMO Inspection

Bioresearch Monitoring (BIMO) inspections were conducted at five domestic clinical investigator study sites participating in the conduct of study protocol 2019nCoV-301: *A Phase 3, Randomized, Observer-Blinded, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-CoV-2 rS) with Matrix-M1™ Adjuvant in Adult Participants ≥ 18 Years with a Pediatric Expansion in Adolescents (12 to < 18 Years).* FDA did not identify any major deficiencies regarding the clinical investigators' conduct of the study, and no data integrity issues were identified. Additionally, FDA's review of the study-wide compliance information from the study did not identify systemic concerns with trial conduct across the other study sites.

8.5 EUA Prescribing Information and Fact Sheets

The Full EUA Prescribing Information, Fact Sheet for Health Care Providers Administering Vaccine (Vaccination Providers), and Vaccine Information Fact Sheet for Recipients and Caregivers were reviewed, and suggested revisions were sent to the Sponsor. The revised Fact Sheets are accurate, not misleading, and appropriate for the proposed use of the product under EUA.

9. Benefit/Risk Assessment in the Context of the Proposed Indication and Use Under EUA

9.1 Known and Potential Benefits

Vaccine effectiveness in participants 12-17 years of age was inferred by immunobridging, based on a comparison of immune responses in participants 12-17 years of age with those of adults 18-25 years of age. The known benefits among vaccine recipients 12-17 years of age relative to placebo are reduction in the risk of COVID-19. The 2-dose regimen of NVX-CoV2373, administered 3 weeks apart, prevented PCR-confirmed mild to severe COVID-19 occurring at least 7 days after the second primary series vaccination in individuals 12-17 years (VE: 78.3% 95% CI: 37.6, 92.5) during the time when the Delta SARS-CoV-2 variant was prevalent, which provides evidence of clinical benefit.

9.2 Uncertainties in Benefits

Effectiveness Against Currently Circulating SARS-CoV-2 Variants

The study enrollment and efficacy follow-up occurred through August 9, 2021, and mainly when the Delta variant of SARS-CoV-2 was predominant and prior to the emergence of Omicron variants. Post-authorization experience with other COVID-19 vaccines has demonstrated substantially decreased effectiveness of a primary series against the currently circulating Omicron variant and sublineages, in particular against milder COVID-19, than was demonstrated in pre-authorization clinical trials conducted when the ancestral strain was circulating. Relevant data to assess effectiveness of NVX-CoV2373 against the Omicron variant and sublineages, including observational data from use in other countries where the vaccine has been deployed, are currently unavailable; however, based on the efficacy estimate in the clinical trial of this vaccine, it is more likely than not that the vaccine will provide some meaningful level of protection against COVID-19 due to Omicron, in particular against more severe disease.

Duration of Protection

The analyses have a limited length of follow up, therefore, it is not currently possible to assess sustained efficacy over a period longer than two months.

Effectiveness in Individuals Previously Infected With SARS-CoV-2

The adolescent expansion study excluded individuals with prior symptomatic PCR-confirmed SARS-CoV-2 infection. However, observational data with other COVID-19 vaccines have demonstrated an added benefit of vaccination to protection conferred by natural immunity (Plumb et al, 2022). Additionally, for individuals previously infected with the Omicron variant of SARS-CoV-2, a vaccine based on the spike protein of the ancestral strain could provide a greater breadth of protection against SARS-CoV-2 variants.

Effectiveness in High-Risk Populations

The available data are insufficient to assess effectiveness in adolescents with some underlying conditions (e.g. immunosuppression) that confer increased risk of severe COVID-19.

Need for a Booster Dose

Based on post-authorization data following primary vaccination with other COVID-19 vaccines in adults, it is likely that booster vaccination following a Novavax COVID-19 primary series would be needed to increase robustness, breadth, and duration of protection against currently circulating and emerging SARS-CoV-2 variants.

Effectiveness in Pediatric Populations

The adolescent expansion to Study 301 enrolled adolescents as young as 12 years of age. Data to directly inform vaccine effectiveness in pediatric age groups younger than 12 years of age were not included or considered as part of this EUA request. If the vaccine is authorized under EUA for use in adolescents, data from studies in younger pediatric age groups could be considered in EUA amendments to expand the authorized use to include those age groups.

Future Vaccine Effectiveness as Influenced by Characteristics of the Pandemic

The continued evolution of the pandemic, including changes in the virus infectivity, antigenically significant mutations to the spike protein, and changes in practice of nonpharmacologic interventions to mitigate against transmission, will likely influence vaccine effectiveness over time. Continued evaluation of vaccine effectiveness following issuance of an EUA and/or licensure will be critical.

Effectiveness Against Long-Term Effects of COVID-19 Disease

Available data are not conclusive on the effectiveness of COVID-19 vaccines currently in use against long-term sequelae of COVID-19 among individuals who are infected despite vaccination. Additional evaluation is needed to assess the effect of this vaccine in preventing long-term effects of COVID-19, including data from clinical trials and from the vaccine's use post-authorization.

Effectiveness Against Asymptomatic Infection and Transmission

Available data for COVID-19 vaccines currently in use has demonstrated that effectiveness against asymptomatic infection is lower and less durable than effectiveness against symptomatic COVID-19. Available data also do not indicate high-level or durable effectiveness against transmission of SARS-CoV-2 from vaccinated individuals with breakthrough infections. Data for these outcomes are not currently available for NVX-CoV2373, it is more likely than not that the observations with other COVID-19 vaccines (with similar antigens and routes of administration) will apply to this vaccine as well.

9.3 Known and Potential Risks

Solicited local site reactions and systemic adverse events were more common after NVX-CoV2373 compared to placebo, with increased frequency and severity following the second dose. Myocarditis/pericarditis is an important identified risk for NVX-CoV2373 as with mRNA COVID-19 vaccines. One SAE of Myocarditis was identified in the adolescent cohort where a 16-year-old male had myocarditis two days after Dose 2 of NVX-CoV2373 in the post-crossover period. Post-authorization studies that directly compare the myocarditis/pericarditis rates in adolescents receiving NVX-CoV2373 and the mRNA vaccines are needed to better understand the risk profiles for different vaccines.

9.4 Uncertainties in Risks

Safety in certain subpopulations

There is insufficient data to evaluate safety of NVX-CoV2373 in subpopulations such as immunocompromised individuals 12-17 years of age and adolescents who are previously infected with SARS-CoV-2. There is also insufficient data to evaluate the safety of the vaccine in children under 12 years old.

Myocarditis/pericarditis

More surveillance studies are needed to characterize the risk of myocarditis/pericarditis in adolescents receiving NVX-CoV2373, for example, to examine if the risk disproportionately affects certain subgroups (e.g., younger males), if the risk is increased with a particular dose in the 2-dose regimen, and to understand the long-term sequelae and outcomes in affected individuals.

Adverse Reactions That are Uncommon or That Require Longer Follow-Up To Be Detected

Following authorization of the vaccine, use in large numbers of individuals 12-17 years of age may reveal additional, potentially less frequent and/or more serious AEs not detected in the trial safety population of approximately 2,100 adolescents. Active and passive safety surveillance studies are needed during the post authorization period to monitor for new safety signals.

10. Overall Summary and Recommendations

Following review of information submitted in support of the EUA request, the review team concludes that:

As summarized in Section 2 of this review, the chemical, biological, radiological, or nuclear (CBRN) agent referred to in the March 27, 2020, EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.

Based on the totality of scientific evidence available, including data from an adequate and well-controlled trial described in Section 6 of this review, the Novavax COVID-19 Vaccine, Adjuvanted, when administered as a 2-dose primary series to individuals 12-17 years of age may be effective in preventing a serious or life-threatening disease or condition that can be caused by SARS-CoV-2. Vaccine effectiveness in participants 12-17 years of age was inferred by immunobridging, based on a comparison of immune responses in participants 12-17 years of age with those of adults 18-25 years of age. Immunobridging statistical success criteria, as described above, were met. The GMR (i.e., adolescents 12-17 years of age versus adults 18-25 years of age) was 1.5 (95% CI: 1.3, 1.7). The difference in SCRs (i.e., adolescents 12-17 years of age minus adults 18-25 years of age) was −1.0% (95% CI: −2.8%, 0.2%). In a descriptive analysis, VE against PCR-confirmed COVID-19 with onset at least 7 days after the second dose was 78.3% (95% CI: 37.6, 92.5) in adolescent participants who were seronegative/PCR-negative at baseline (pre-Dose 1).

Based on the data summarized in Section 6 of this review and assessment of benefits and risks in Section 9 of this review, the known and potential benefits of the vaccine outweigh the known and potential risks of the vaccine when used for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12-17 years of age. Known benefits include reduction in the risk of confirmed COVID-19 occurring at least 7 days after Dose 2. Potential benefits that

could be further evaluated but are not necessary to support an EUA include prevention of COVID-19 in individuals with previous SARS-CoV-2 infection, prevention of mortality and long-term complications of COVID-19, reduction in asymptomatic SARS-CoV-2 infection and reduction of SARS-CoV-2 transmission. Uncertainties related to benefits include effectiveness against currently circulating and future SARS-CoV-2 variants; effectiveness against long term effects of COVID-19 disease; and duration of protection. Known risks include myocarditis/pericarditis, common local and systemic adverse reactions and lymphadenopathy related events, chills, diarrhea, and decreased appetite. Uncertainties and potential risks that should be further evaluated include safety in certain subpopulations (including younger age groups), characterization of the risk of myocarditis and pericarditis, and adverse reactions that are uncommon or that require longer follow-up to be detected.

As summarized in Section 3 of this review, mRNA-based vaccines Comirnaty and Spikevax are the only FDA-approved vaccines indicated for active immunization for prevention of COVID-19 caused by SARS-CoV-2. Comirnaty is the only COVID-19 vaccine approved for use in individuals 12-17 years of age. Authorization of the Novavax COVID-19 Vaccine, Adjuvanted would provide an alternative vaccine platform (recombinant protein plus adjuvant) to prevent COVID-19 caused by SARS-CoV-2 for individuals 12-17 years of age who, for example, have contraindications to the approved mRNA-based vaccines.

Based on the considerations outlined above, the review team recommends issuance of an EUA for use of the Novavax COVID-19 Vaccine, Adjuvanted for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12-17 years of age.

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12. Appendix A. Potential Immune-Mediated Medical Conditions

Table 21. Potential Immune-Mediated Medical Conditions, Study 301

Category	Diagnoses (as MedDRA Preferred Terms)
Neuroinflammatory disorders	Acute disseminated encephalomyelitis (including site-specific variants: e.g., non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculomyelitis), cranial nerve disorders including paralyses/paresis (e.g., Bell's palsy), generalized convulsion, Guillain-Barre syndrome (including Miller Fisher syndrome and other variants), immune-mediated peripheral neuropathies and plexopathies (including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy), myasthenia gravis, multiple sclerosis, narcolepsy, optic neuritis, transverse myelitis, uveitis.
Musculoskeletal and connective tissue disorders	Antisynthetase syndrome, dermatomyositis, juvenile chronic arthritis (including Still's disease), mixed connective tissue disorder, polymyalgia rheumatic, polymyositis, psoriatic arthropathy, relapsing polychondritis, rheumatoid arthritis, scleroderma (including diffuse systemic form and CREST syndrome), spondyloarthritis (including ankylosing spondylitis, reactive arthritis [Reiter's Syndrome] and undifferentiated spondyloarthritis), systemic lupus erythematosus, systemic sclerosis, Sjogren's syndrome.
Vasculitides	Large vessels vasculitis (including giant cell arteritis such as Takayasu's arteritis and temporal arteritis), medium sized and/or small vessels vasculitis (including polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg–Strauss syndrome [allergic granulomatous angiitis], Buerger's disease [thromboangiitis obliterans], necrotizing vasculitis and ANCA-positive vasculitis [type unspecified], Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis).
Gastrointestinal disorders	Crohn's disease, celiac disease, ulcerative colitis, ulcerative proctitis.
Hepatic disorders	Autoimmune hepatitis, autoimmune cholangitis, primary sclerosing cholangitis, primary biliary cirrhosis.

Category	Diagnoses (as MedDRA Preferred Terms)
Renal disorders	Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis).
Cardiac disorders	Autoimmune myocarditis/cardiomyopathy.
Skin disorders	Alopecia areata, psoriasis, vitiligo, Raynaud's phenomenon, erythema nodosum, autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis), cutaneous lupus erythematosus, morphoea, lichen planus, Stevens-Johnson syndrome, Sweet's syndrome.
Hematologic disorders	Autoimmune hemolytic anemia, autoimmune thrombocytopenia, antiphospholipid syndrome, thrombocytopenia.
Metabolic disorders	Autoimmune thyroiditis, Grave's or Basedow's disease, new onset Hashimoto thyroiditis, diabetes mellitus type 1, Addison's disease.
Other disorders	Goodpasture syndrome, idiopathic pulmonary fibrosis, pernicious anemia, sarcoidosis.

Source: Adapted from protocol 2019nCoV-301 Table 11. IND 22430.
Abbreviations: ANCA=anti-neutrophil cytoplasmic antibody; CREST=calcinosis, Raynaud's phenomenon; esophageal dysmotility; sclerodactyly, telangiectasia; IgA=immunoglobulin A; MedDRA=Medical Dictionary for Regulatory Activities